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ANNALS OF
INTERNAL MEDICINE

VOLUME 22 JUNE, 1945 NUMBER 6

HIRSUTISM IN FEMALES; A CLINICAL STUDY OF ITS ETIOLOGY, COURSE AND TREATMENT *

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Boston, Massachusetts

THE bearded lady has always been a subject of lively interest. To the public she is amusing, to the showman profitable, to the physician physiologically fascinating—and to herself, utterly miserable. Many instances of virilized women may be found in the literature, most of whom have been suffering from adrenal, pituitary, or ovarian tumors. The earliest of these reports are little more than clinical observations, some with appended pathological findings. Later, improved chemical and biological technics often aided in discovering the site of the disturbance. In spite of our increased knowledge of endocrine physiology, however, much of the information is still conflicting and obscure.

Despite the voluminous literature concerning functional endocrine tumors, their actual occurrence is fairly rare. In contrast, the occurrence of hirsute women is common. In the past two years, we have seen more than 200 such patients. Most of them have come to us with complaints which were mainly cosmetic. As their histories were analyzed, however, the altered emotional state became a most striking feature. As a result of their masculine appearance, often in the presence of thoroughly feminine inclinations, many were pitiful neurotics.

In contrast with the many reports of masculinization resulting from functioning tumors, is the paucity of information regarding this type of "idiopathic" malady. We believe that this neglected type of hirsutism represents the most important variety of the disease, because of its much commoner occurrence. Accordingly, we decided to select at random a group of bearded women and to conduct certain investigations of their endocrine status. Only through numerous studies of this type will information be

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obtained sufficient to clarify the problem and to indicate a satisfactory method of therapy, which is so sorely needed.

Before reporting our findings it may be well to consider briefly the subject of hair growth. A few pertinent experiments on animals demonstrate the following facts. Well-fed adrenalectomized rats [1] demonstrate precocious hair growth. Underfed normal rats have delayed growth of hair even when skeletal growth continues.[2] In these underfed animals the adrenals hypertrophy, and removal of these enlarged glands causes growth of new hair within 40 hours after adrenalectomy.[3] Administration of estrogens retards hair growth in rats,[4] guinea pigs [5] and dogs.[4] Concomitant administration of androgens prevents this effect in rats.[5] Gonadectomy in fowls often causes changes in plumage, which in birds is somewhat analogous to hair.[6] Pituitarectomy and thyroidectomy have been shown to exert influence upon the piliary system of various animals.

Important as is this work in demonstrating some degree of hormonal control on mammalian hair growth, most of it is not applicable to man whose piliary system is unique in several ways. The most obvious sign of this dissimilarity is the marked difference in hair development on contiguous body areas in man. Thus any discussion of human hair growth should include consideration of (1) hair growth per se, and (2) possible secondary influences. Much of the work on the first subject has been performed, and recently reviewed by Danforth.[7] He states that although humoral control of human hair growth probably exists, the final product of each individual follicle is largely determined by constitutional factors within the hair cell itself. Thus, considering the humoral complexes of the male as one factor, and of the female as another, there are some follicles unaffected by the difference, while in others the effect may range from slight to profound. In other words, there is a constitutional gradient of response of each individual follicle to the hormonal influences which are presumed to be equally accessible to all. This might explain why two morphologically identical follicles may produce fine body hair until puberty, when the product of one changes to long terminal hair, while the product of the other continues unchanged throughout life.

On the basis of this concept, Danforth [7] offers the following classification of hair. *First, general body hair* ("lanugo" or "vellus"), which is uninfluenced by endocrine factors. *Secondly, ambosexual hair,* present in males and females, but dependent on hormonal stimulation which is apparently equivalent in both sexes. The axillary and pubic hair exemplify this type. *Thirdly, truly sexual* hair, represented by the beard of the male, and less clearly by the terminal hair of the shoulders, anterior chest and abdomen. The head hair, or *capitus,* is probably a secondary sexual characteristic also, since its weight per unit of length is greater in males.[8]

The adrenal cortex, gonads, thyroid and anterior pituitary are the endocrine glands mainly concerned with hair production. The influence of the adrenal cortex on female ambosexual hair growth has recently been empha-

sized.[9] In pan-hypopituitarism and in Addison's disease, conditions in which the adrenal cortex is virtually non-functioning, axillary and pubic hair is absent. The adrenal cortex in hypo-ovarian dwarfs, although present, is of subnormal size; likewise, the axillary and pubic hair is present but diminished in amount. The ovaries and anterior pituitary apparently exert no direct influence on ambosexual hair growth in the female. This is proved by cases of Addison's disease with adequate ovarian and anterior pituitary function,[9, 10] which never developed pubic or axillary hair. The maintenance of ambosexual hair after the menopause is also an indication of the absence of ovarian influence. Prepubertal ovariectomy results in absent axillary and pubic hair but this is probably due to secondary lack of stimulation of the adrenal cortex by estrin.[9, 11]

In the male, there may be more complicated factors influencing the growth of ambosexual hair. Males with panhypopituitarism, and thus, secondary adrenal cortical and gonadal hypofunction, have little or no axillary or pubic hair. Men with Addison's disease have sparse pubic and axillary hair. Prepubertal castration does not prevent the appearance of ambosexual hair, although it may not be abundant.[12] Testosterone has been found to increase the size and number of the pubic sebaceous glands in prepubertal boys.[13] It would appear that male ambosexual hair growth is apparently conditioned by a synergism between the gonads and adrenals.

The beard of the male would seem to be influenced chiefly by testicular secretions. Supporting this assumption is the absence of the beard in prepubertal castrates and its disappearance following postpubertal castration. Hypopituitary males, who have secondary hypogonadism, likewise have no beard. Men suffering from Addison's disease do not experience such loss.

The ambosexual hair in both sexes, and the beard in males, are diminished or absent in myxedema. This may be due in part to the secondary hypogonadism known to accompany this disease.[14] The major cause, however, is probably the generalized hypometabolism which affects not only the individual follicle growth, but also the function of the other endocrine glands.

Although the general body hair is supposedly uninfluenced by endocrine factors,[7] clinical observation would seem to indicate that this is not entirely true. One of the characteristic features of patients suffering from panhypopituitarism is the virtual absence of body hair. Some cases of Addison's disease have scanty or absent body hair. Individuals with anterior pituitary hyperfunction are frequently hairy. Patients who have had ovarian and adrenal tumors removed[15, 16] frequently demonstrate postoperative diminution of their body hair. It would seem that under certain circumstances even the *vellus* is conditioned by endocrine stimulation. These effects may, of course, be mere reflections of a generally altered metabolism.

The foregoing facts seem to indicate that there are two major influences on hair growth, one constitutional, the other humoral. The *constitutional factor* is the capability of response of each individual follicle to endocrine stimuli. The *humoral factor* represents the various hormones supplying the

stimulus for hair production to those follicles inherently sensitive to their action. Other local factors, such as follicular nutrition, nerve and blood supply must also exert their effect.

Since the control of normal hair growth is still obscure any discussion of the causes of pathological hair growth is difficult. Hirsutism is defined as excessive hair growth, but there is no clearcut distinction as to what type of hair is involved. Also, there is a tremendous variation in the quantity and distribution of body hair in normal subjects. Danforth's studies [17] indicate that about one-third of the apparently normal white females have hypertrichosis. Redlich [18] has classified hair distribution in the male, but he included only body-hair patterns, which are presumably less affected by endocrine factors.

Although lacking in precise definition, hirsutism has been reported with many pathological entities. The best recognized of these are basophilic tumors of the anterior pituitary (Cushing's disease) and neoplasm and hyperplasia of the adrenal cortex (adrenocortical syndrome, adrenogenital syndrome, or Cushing's syndrome). Also associated with hirsutism are arrhenoblastomata of the ovary,[19] thymic tumors (with secondary adrenal hyperplasia),[20, 21] lutein cell tumors,[22] and diffuse luteinization of the ovaries.[23] Schwartz [24] quotes some of the continental literature reporting hirsutism associated with teratoma, neuritis, mumps, and encephalitis. It has been described not infrequently accompanying low mentality states, and multiple sclerosis.

Permanent hirsutism may also accompany certain physiological processes. It may accompany or immediately follow menarche, childbirth or menopause. Genetics may also influence hair growth. Some families may be hirsute almost from birth. Likewise, certain races, notably the Jews and Italians, appear particularly affected. Hirsutism may also be transient. It may accompany pregnancy and disappear postpartum. Recently we have noted its occurrence in two cases of severe burns. It may also appear during therapy with dilantin [25] and testosterone.[26]

It may be seen that *hirsutism* is a malady of unclear definition, and complex etiology. In this paper, for purposes of clarity, we shall confine our discussion to female hirsutism, which will connote the presence of a beard, associated with altered ambosexual hair-growth, unless otherwise stated. Much of the current opinion seems to consider adrenal cortical malfunction as the greatest single factor concerned in the hirsute syndromes. Our observations were made with this premise in mind.

Clinical Material

Thirty-three patients have been observed during a period of three years. Actually, we encountered scores of patients during that time, but many were unwilling to permit adequate study, or did not satisfy the above criteria of hirsutism.

When first seen, the patients ranged from 19 to 67 years of age. Twenty-two of the group were married and the majority were hirsute before their marriage. Most of the group were brunette and tended to be swarthy. One patient, however, was a light blonde (I. K.) and her abnormal hair was of the same hue. There were six Jews and five Italians. One patient (P. W.) was a negress, which is interesting in the light of a recent article which states that hirsutism does not exist in this race.[24]

Since hirsutism occurs either in the presence of some pathologic lesion, or as an abnormal response during some physiological state, we employed the following classification in cataloging our patients.

I. *Permanent Hirsutism*
- A. Pituitary
- B. Adrenal cortex
- C. Gonads
- D. Hypothalamus
- E. Other lesions (pinealoma, thymoma, etc.)
- F. Idiopathic *
  1. Postpubertal
  2. Postpregnancy
  3. Postmenopausal
  4. Genetic
     - a. Familial
     - b. Racial
  5. Unclassified

II. *Transient Hirsutism*
- Pregnancy
- Therapeutic
- Other causes (burns, etc.)

In our series of 33 patients, 29 fall into "the idiopathic" class. Of these, 20 are of the postmenarcheal type, four postpregnancy, two postmenopausal, two familial, and one unclassified. Four additional patients (one pseudohermaphrodite, one acromegalic, and two cases of transient hirsutism) are discussed separately.

"Idiopathic" Hirsutism. Twenty-four of these 29 women had heavy beards, which required daily shaving (figure 1). All but four of these displayed marked hypertrichosis on other parts of the body (figure 2). The abnormal hair was coarse and wiry. The majority had increased hair over the forearms and thighs; usually an increase over the shoulders, and occasionally about the nipples and between the breasts. In 23 subjects the pubic hair distribution was distinctly male. One patient (F. M.) had auburn head, pubic and axillary hair. Soon after puberty she developed an extension of her pubic hair over her abdomen. Two distinct abdominal triangles with opposing bases resulted, one of auburn hair, representing the original

* "Idiopathic" is used in this paper to denote cases in which the primary etiologic factor causing the hirsutism was not clearly demonstrable. Undoubtedly some of these cases might be classified as adrenogenital syndrome, etc., but the authors prefer to consider them in a less confining category, until better diagnostic proof is established.

normal female distribution, and the other of black hair, indicating the more recently acquired male escutcheon!

Two of our patients, each Italian, were excellent examples of familial hirsutism. One (A. M.) had three hairy sisters, a hirsute mother and grandmother. She had heavy facial hair, male pubic hair distribution, and marked increase in hair over her extremities and shoulders. The other patient (L. M.) had five daughters and several granddaughters who showed marked generalized hirsutism. Even the five year old granddaughter of this patient had a well-defined moustache and beginning facial hirsutism.

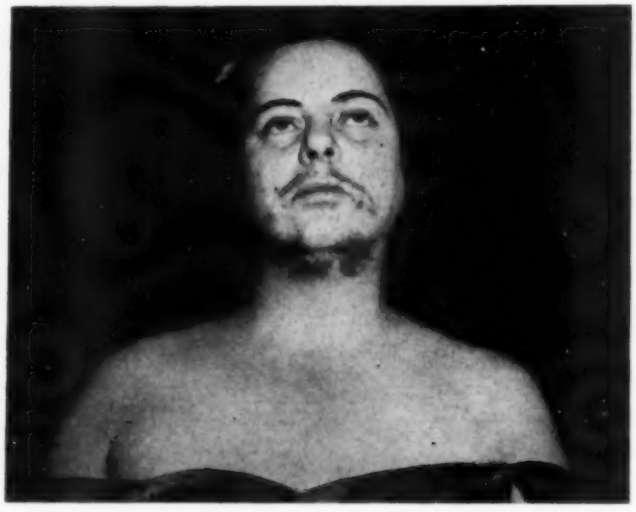

FIG. 1. (Case L. T.) This patient's beard is the result of not having shaved for about 48 hours. Note the acne and seborrhea of the skin.

None, however, displayed male pubic hair. In both of these families the hair tended to be more silky and finer in texture than in the patients with other types of hypertrichosis. It was similar to excess "lanugo" hair described in the famous Jefticheff and Schwe Maong families of "dog men." [17]

Two patients were representatives of the postmenopausal type. Both had typical sparse, long, curly chin hair and well-marked moustaches. Otherwise their body hair was normal.

Two patients (M. J. and M. M.) displayed moustaches only, unassociated with abnormal body hair. They were included because of the large number of women seen with this type of abnormality.

Signs and Symptoms Related to the Sexual System. Aberration in sexual structure and function is an integral part of hyperadrenocorticism. In Cushing's syndrome, there is presumably an overproduction of steroids concerned chiefly with gluconeogenesis, with little involvement of the androgenic components of the cortex.[27, 28] It is classically associated with weakness, genital and breast atrophy, and sexual underfunction. The adreno-

genital syndrome involves an overproduction of androgenic, anabolic factors, and is associated with increased strength, good musculature, and genital hypertrophy.

The effects of androgenic overproduction depend upon the time of its occurrence. If the process begins in utero, pseudohermaphroditism results:

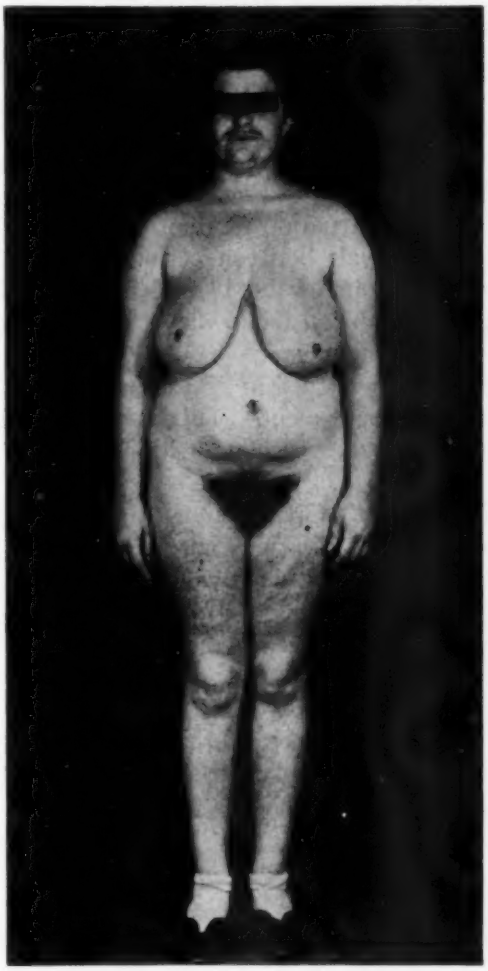

FIG. 2. (Case S. L.) Typical patient with "idiopathic" hirsutism. Note the male pubic hair distribution and the hirsutism of the face and extremities. The breasts are hypertrophied.

if it is delayed until sexual maturity is attained, the adrenogenital syndrome ensues. An enlarged clitoris is one of the classic signs of this latter disease. Formerly [29] it was considered one of the diagnostic criteria, but recently it has been pointed out that there may be a great overlapping of signs, many cases of Cushing's syndrome displaying features of the adrenogenital syndrome and vice versa.[30]

The clitoris was definitely enlarged in 11 of these patients. In each there was also a male configuration of pubic hair. They were among the most bearded of the group. It is of interest to note that in our series, although a male pattern of pubic hair distribution sometimes occurred without clitoral enlargement, the reverse was not encountered.

In 15 patients the labia majora were hypertrophied, giving a pouting, or ballooned appearance. This was usually accompanied by clitoral hypertrophy, but in a few patients (S. DeA., L. S., S. L., G. K., M. J.) it appeared to be the only abnormality of the external genitalia. Two (S. DeA. and S. D.) had infantilism of the internal pelvic structures. Another (L. T.) was found to have atrophic ovaries at operation. The rest had apparently normal internal pelvic organs.

In these 29 patients menstruation was normal in 16, and irregular in 12, often with six-month intervals between periods. One patient (S. DeA.) had never menstruated. Four of the 11 patients with clitoral enlargement had perfectly normal periods. Libido was low or absent in 12 patients, apparently normal in the remainder.

The breasts were well-developed in 27 patients; in fact, there was a tendency toward increased development. This is of interest inasmuch as the adrenocortical syndromes are associated with lack of breast development, or breast atrophy.

Other Physical Findings. Obesity is a counterpart of adrenal cortical hyperfunction, especially the Cushing syndrome. Recently, however, it has been emphasized that this obesity is not extreme and may be merely a redistribution of fat, which may give a superficial appearance of obesity.[31] The actual weight of children with adrenocortical obesity is not greatly increased over the average.[32] That adrenal cortical "obesity" is actually fat and not merely tissue fluid is recently reported.[33]

In our group, obesity was generally characteristic. Only seven patients were thin. By comparing the actual weight with the ideal weight of each patient for her height and age, it was found that there was an actual increase in weight present (chart 1).

The fat in our patients was largely confined to the trunk. The arms and legs were inclined to be normal or even slender. Most of the group had broad faces, thick necks and heavy shoulders. Usually the abdominal fat panniculus was increased, and the hips broad and fat. In none was the fat painful to pressure. The obesity did not seem refractory to weight reduction.

Thin skin with prominent veins has been noted in Cushing's syndrome. Although an occasional patient demonstrated prominent venous patterns over the breasts, only one (E. M.) had an integument of the type seen in Cushing's syndrome; she showed many other manifestations of this syndrome. It is often assumed that acne is related to excessive androgen formation [34] and acneiform lesions are frequently described with Cushing's syndrome. Marked acne was observed in five of this group, slight acne in two others.

It is of interest that the two patients with most severe acne had the least concomitant virilism (K. C., R. M.).

Reddish-purple striae on the abdomen and shoulders were noted in seven patients. Eight of the group complained of the appearance of ecchymoses upon relatively slight trauma.

Benign hypertension was found in six patients, all of whom were over 42 years of age.

Results of Sugar Tolerance Tests. Mild diabetes is one of the features of certain types of increased adrenal cortical function. It has been shown that some of the cortical hormones promote gluconeogenesis.[34] Since there is thought to be excessive production of such adrenal cortical hormones in Cushing's syndrome, the diabetes accompanying that disease has been attributed to the increase in gluconeogenesis coupled with an inhibition of the tissue anabolism.[27, 28]

The diabetes of hyperadrenalcorticism is insulin-resistant. Recently, Fraser, et al.[36] have devised a glucose and insulin tolerance test, based on tests developed by Himsworth.[37] The procedure consists of the simultaneous oral administration of glucose, with sufficient insulin given intravenously to insure its utilization. The resulting blood sugar curve, taken at 30-minute intervals, is essentially a straight line in normals and in insulin-sensitive diabetics. In individuals with insulin insensitivity, there is a rise in the blood sugar level simulating a diabetic type of oral glucose tolerance curve. This test has been found positive in cases of Cushing's disease.[36, 38]

The test was performed on all of our cases by administering to each, in a fasting state, 100 grams of glucose by mouth, followed immediately by the intravenous injection of regular insulin (0.1 unit per kilogram of body weight). (This is the technic advised by Fraser except that four blood specimens were taken at 30-minute intervals, after the fasting specimen.) Since the test may be influenced by the preceding diet,[39] each patient had taken a high carbohydrate diet for at least three days before the procedure.

Five of our patients had classical diabetes mellitus. All were insulin-insensitive as measured by the foregoing test. Fourteen of the remaining 24 showed abnormal glucose-insulin tolerance curves (figure 3). It may be seen that in all patients the blood sugar level at 60 minutes was well above the fasting level and in most had not yet returned to the fasting value at the end of two hours. All of the patients except one (M. L.) were obese. Of the normal curves obtained, two patients were very slender, and the rest somewhat overweight but not to the degree of the foregoing group.

The greater frequency of abnormal glucose and insulin tolerance tests in the obese hirsute women led to the performance of similar tests on patients who were merely obese. Three men, weighing 205, 263, and 286 pounds, and two women weighing 180 and 175 pounds, were studied. None exhibited abnormal hair growth or had any symptoms or signs referable to hyperadrenocorticism. All of these patients also had abnormal glucose insulin tolerance curves (figure 3).

CHART I

Summary of Findings of 29 Cases of "Idiopathic" Hirsutism

Number	Initials	Age	Married	Actual Wgt.	Ideal Wgt.	Height	Onset Disease	Catamenia				Hirsutism							Large Breasts	Obesity	Early Strength	Later Weakness	Acne	Striae	Prominent Veins	Brutisability	Glycosuria	Renal Stones	Hypertension	17-ketosteroids mg./24 hours
								Normal	Amenorrhea	Irregular	Menopause	Libido	Pregnancies	Face	Arms, Legs	Male Pubic Escutcheon	Clitoris	Hypertrophied Labia												
Post-Menarcheal Hirsutism																														
1	S. W.	29	+	213	126	63	16	−	−	+	−	L	0	+	+	+	+	+	+	+	+	+	0	0	0	0	0	0	0	4.8 8.2
2	I. K.	30	+	190	131	64	18	−	−	+	−	N	+	+	+	+	+	0	++	++	−	−	0	0	0	0	0	0	0	14.9
3	M. M. U.	25	−	180	125	63	24	+	−	−	−	N	0	+	−	−	N	0	+	+	0	0	0	0	0	0	0	0	0	2.2 8.5
4	S. deA.	56	+	243	135	61	−	−	+	−	−	0	0	+	+	+	N	+	+	+	+	+	+	0	0	0	0	0	0	8.7
5	C. McL.	32	+	137	121	60	14	+	−	−	−	N	+	+	+	+	N	0	+	+	+	0	+	+	0	0	0	0	0	3.5 3.2
6	R. M.	21	−	110	120	62	14	+	−	−	−	N	0	+	−	+	N	0	+	0	0	0	0	0	0	0	0	0	0	3.4
7	J. D.	27	−	200	159	72	13	+	−	−	−	N	0	+	+	+	+	0	+	+	+	0	0	0	0	0	0	0	0	−
8	M. L.	19	−	137	139	68	17	−	−	+	−	N	0	+	+	+	+	+	0	0	+	+	0	0	0	0	0	+	0	17.7 13.7
9	K. McG.	52	+	178	138	62	14	+	−	−	+	L	+	+	+	+	N	0	+	+	0	+	+	+	0	0	+	0	+	3.2 2.4
10	M. F.	21	−	161	133	66	13	+	−	−	−	N	0	+	+	+	+	+	+	+	0	0	0	0	+	0	0	0	0	13.0
11	F. M.	25	−	96	117	60	20	−	−	+	−	N	0	+	+	+	N	0	++	0	0	0	0	0	0	0	0	0	0	14.3
12	A. A.	56	+	200	133	60	16	−	−	+	−	N	0	+	+	+	+	+	++	++	+	+	+	+	0	+	+	0	+	1.7
13	K. C.	21	−	131	133	66	14	−	−	+	−	N	0	+	+	+	N	+	0	0	0	0	0	0	0	0	0	0	0	2.0 5.4
14	H. F.	23	−	186	134	66	14	−	−	+	−	N	0	+	+	+	N	+	+	+	+	0	0	0	0	+	0	0	0	10.1
15	M. M.	53	+	250	134	68	17	−	−	+	−	N	+	+	+	−	N	0	+	+	+	0	0	0	+	0	0	+	0	6.3 7.2
15	S. D.	35	+	216	150	68	16	−	−	+	−	L	0	+	+	+	N	0	+	+	+	0	0	0	0	0	0	0	0	17.6
17	L. S.	23	−	227	157	72	14	+	−	−	−	L	0	+	+	+	N	+	+	+	+	0	0	0	0	0	0	0	0	4.4 9.8
18	S. L.	25	+	120	113	58	21	+	−	−	−	L	0	+	+	+	N	+	+	+	+	+	0	+	0	0	0	0	0	4.9
19	P. W.	42	+	200	133	62	17	+	−	−	−	N	+	+	+	+	N	+	+	+	+	0	0	0	0	0	0	0	+	0.9
20	G. K.	44	+	135	133	61	17	+	−	−	−	L	+	+	+	+	N	+	+	0	+	0	0	0	+	0	0	0	0	3.8 3.2

CHART I—*Continued*

Number	Initials	Age	Married	Actual Wgt.	Ideal Wgt.	Height	Onset Disease	Catamenia				Hirsutism							Large Breasts	Obesity	Early Strength	Later Weakness	Acne	Striae	Prominent Veins	Bruisability	Glycosuria	Renal Stones	Hypertension	17-ketosteroids mg./24 hours
								Normal	Amenorrhea	Irregular	Menopause	Libido	Pregnancies	Face	Arms, Legs	Male Pubic Escutcheon	Clitoris	Hypertrophied Labia												
Post-Pregnancy Hirsutism																														
21	D. N.	27	+	197	129	64	25	−	−	+	−	N	+	+	+	+	+	+	+	+	0	0	+	0	+	0	0	0	0	2.7
22	J. McD.	34	+	137	121	60	31	+	−	−	−	N	+	+	+	+	+	+	+	0	0	0	0	0	+	+	0	0	0	11.2
23	E. M.	42	+	164	128	60	32	−	−	+	−	L	+	+	+	+	+	+	+	+	0	0	+	+	+	+	+	0	+	24.0
24	M. J.	45	+	242	141	64	41	+	−	−	+	N	+	+	−	−	N	+	+	+	0	0	0	+	+	+	+	0	0	14.3 5.6
Post-Menopausal Hirsutism																														
25	G. L.	67	+	182	152	66	47	+	−	−	+	L	+	+	−	−	N	0	+	+	0	0	0	0	+	+	0	0	0	0.2
26	A. McG.	51	+	169	138	62	35	+	−	−	+	L	+	+	−	−	N	0	+	+	0	0	0	0	0	0	0	0	+	2.8
Familial Hirsutism																														
27	L. M.	61	+	168	140	63	B.	+	−	−	+	L	+	+	+	−	N	0	+	+	0	0	0	0	0	0	+	0	+	1.8
28	A. M.	23	+	221	121	61	B.	+	−	−	−	N	+	+	+	+	N	0	+	+	+	0	0	0	0	0	0	0	0	0.5
Unclassified																														
29	L. T.	33	+	135	133	64	25	−	−	+	−	L	0	+	−	+	N	0	+	0	0	+	+	0	+	+	0	0	0	12.0 6.8

Key: N = Normal, B = Birth, L = Low, O = Absent

We attempted to improve the test by giving both the glucose and insulin intravenously, using 25 grams of glucose in a 50 per cent solution [40] and 0.1 unit of regular insulin per kilogram of ideal body weight. The results obtained in a few cases showed very inconstant responses, but there was no evidence of insulin insensitivity.

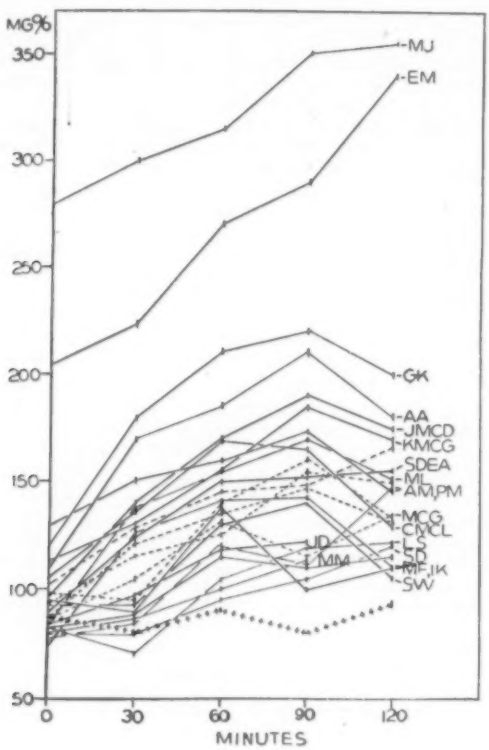

FIG. 3. Glucose and insulin curves of patients showing tendency towards insulin resistance. ++++ Normal curve. ——— Hirsute patients. - - - - Obese patients without hirsutism.

An evaluation of the glucose-insulin tolerance test as a clinical procedure is not pertinent to the general subject under consideration. However, the possibility of the test being abnormal in some cases of simple obesity should be remembered. Since obesity is present in Cushing's syndrome, and since Himsworth and Kerr [38] have pointed out that "the insulin-insensitive diabetics . . . tend to be older, obese . . ." it may be asked if the abnormal curves obtained were not conditioned somewhat by the presence of overweight.

17-ketosteroids. The urinary 17-ketosteroids are (by definition) those steroids possessing a methylene and a ketone group at the seventeenth carbon atom which enables them to combine with meta-dinitro-benzene (in the presence of alkali) to produce a pink color. In the female it is believed

that all of the 17-ketosteroids are produced by the adrenal cortex. Their determination would seem to furnish an index of adrenal cortical function in the female.

The 17-ketosteroid which represents the urinary end products of androgen metabolism are found in the neutral (non-phenolic) fraction of hydrolyzed urine. Estrone, also a 17-ketosteroid, is removed with the phenolic and the acid fractions, by treatment with alkali. The remaining material represents the alcoholic alpha and beta ketosteroids, and a non-alcoholic fraction. The beta ketosteroids are precipitated by digitonin which gives a means of separation. The total and alpha ketosteroids are increased in cases of adrenal hyperplasia and adrenal cancer.[41, 42, 43] It is believed that the beta and non-alcoholic fractions are elevated only in cases

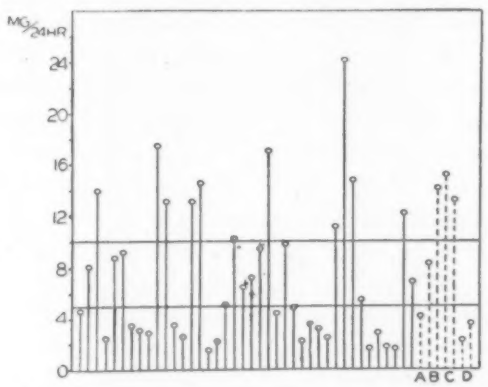

FIG. 4. 17-ketosteroid excretions in cases of hirsutism: A—Acromegalic. B—Pseudohermaphrodite. C, D—Transient hirsutism of pregnancy. The rest are cases of "idiopathic" hirsutism.

of carcinoma of the adrenal cortex.[42, 43] The 17-ketosteroids were determined in our cases according to methods which have been employed in this laboratory for several years.[41, 44] In some instances, alpha fractions were determined, so that an estimate of the beta and non-alcoholic fractions might be obtained. The latter were not further separated. In this laboratory, the normal range of excretion of total ketosteroids in adult females is from 5 to 10 mg. per 24 hours. Collections were always made when the patients were in excellent health and free of the most trivial infections, since even mild infectious states are known to lower steroid output. It will be noted that the great majority of these patients had 24-hour 17-ketosteroid excretions within the normal range, or in a range considered definitely subnormal for adult women (figure 4). This latter finding has surprised us considerably, and we are unable to explain it. Somewhat high values were found in four patients (E. M., M. L., L. T., and S. D.) all of whom showed severe virilizations. Three patients (I. K., M. F. and F. M.) also exhibited slightly elevated values. The first two of these exhibited hypertrophy of

the clitoris. The third patient was slim, and although she had a male hair distribution, complained only of infrequent menses. In a few cases in which beta fractions were obtained, the results were normal.

Radiographic Studies. Roentgenograms of the skull, sella, spine, pelvis, and long bones were obtained in each case. In each, the sella turcica was normal. No abnormalities were detected in the long bones, or epiphyses. Two patients showed slight osteoporosis of the spine. One of these (A. McG.) probably had postmenopausal osteoporosis, while the other patient (E. M.) had Cushing's syndrome. The latter patient also showed slight decalcification of the skull.

All patients had flat films of the abdomen for kidney outline and position. If any displacement was noted, intravenous or retrograde pyelography was then employed. In none was there any finding suspicious of adrenal tumor or hyperplasia. Two (M. L., M. Me) showed the presence of renal calculi; the first, bilateral, the second, unilateral. In both, pyelotomy was performed because of renal colic. We did not feel that perirenal air injections for roentgenographic studies were justified in most of these cases.

Other Laboratory Data. Fourteen of this group had one or more basal metabolic rate determinations, all within normal limits. Qualitative tests of the urine (Sulkowitch test) showed no evidence of hypercalcinuria save in one case (M. L.). Red blood cell counts and hemoglobin determinations gave no evidence of polycythemia. In seven of the more severe cases, estimations of sodium, potassium, chloride and CO_2 were performed, but no deviation from the normal was observed.

Estimations of gonadotropins were made in several cases. It is interesting that in two instances (P. W., G. K.), although the patients were still menstruating, assays of the urine for the follicle stimulating hormone showed that more than 10 rat units were excreted per 24 hours, indicating hyperfunction of the pituitary gland. Roentgen-rays of the sella turcica were normal in both instances.

As we mentioned above, most of the cases came to us with complaints chiefly related to the disturbing cosmetic or psychic effects of hirsutism. Three patients, however, seemed to represent classical adrenal cortical syndromes. Their histories are given in detail. Some of the many problems involved in the establishment of an etiology of hirsutism and the difficulties encountered in the treatment of these individuals are illustrated in the following cases.

Case Reports

Case 1. M. L., a 19 year old student nurse, was admitted to the hospital May 27, 1941, because of a typical attack of renal colic on the left. At the age of 12 she began to have painless menstrual periods of eight days' duration occurring at intervals of two to four months. For five months before this hospitalization she had had no menses. At 17 she noticed an abnormally large amount of hair on her face, abdomen, arms and legs. Soon it became necessary for her to shave daily. She

presented a striking configuration (figure 5) in that she had a large head and neck, broad shoulders, and narrow hips. The excess adipose tissue in the head and neck stood out in great contrast to very small amounts elsewhere. The breasts were rela-

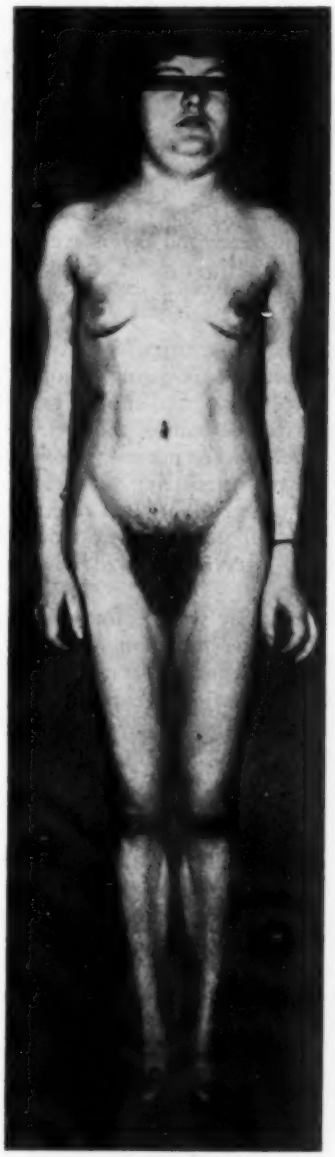

FIG. 5. (Case M. L.) Note the large head and neck, broad shoulders, narrow hips, small breasts, male escutcheon, and prominent muscles.

tively small. Many muscle patterns in the extremities were readily noticeable. She weighed 137 pounds and was 68 inches tall. There were patches of brown pigment over the chin, neck, axillae, areolae, breasts and abdomen. A heavy beard was present and there was a moderate increase of coarse black hair over shoulders, extremities,

and abdomen. A male escutcheon was noted. There were no striae. Acne was not present. The blood pressure was normal. The labia majora were distinctly large and pouty and the clitoris was twice normal size. The uterus and ovaries seemed to be normal.

Red, white and differential blood cell counts were normal. The urine contained a small number of red and white blood cells but no albumin or sugar. *B. coli* were cultured from the urine. The Sulkowitch test for calcium gave a strong reaction even after the patient's diet had contained only a small amount of calcium for three days. Blood chemical studies showed the sodium to be 141 m. eq. per liter, potassium 4.5 m. eq. per liter, non-protein nitrogen 34 mg. per 100 c.c., calcium 10.2 mg. per 100 c.c., phosphorus 3.8 mg. per 100 c.c., phosphatase 3.4 Bodansky units, cholesterol 154 mg. per 100 c.c. and total protein 7.1. gm. per 100 c.c. Roentgenograms of the sella turcica, chest, hands, humeri, femora, and pelvis were normal. The development of the bones was in accordance with the age of the patient. Pyelograms showed two small calculi in the left renal pelvis, and a small one in the right renal pelvis, but no displacement of either kidney.

The glucose-insulin tolerance test, using 6 units of insulin intravenously and 65 grams of glucose by mouth, gave the following changes in blood sugar: 87, 119, 133, 143, 142, 143, and 147 mg. per 100 c.c., the specimens having been taken at 0, 20, 30, 45, 60, 90, and 120 minutes after beginning the test. The basal metabolic rate was plus 2 per cent. The visual fields were normal. An assay of a 24-hour specimen of urine for 10 rat units of follicle stimulating hormone was negative. The excretion of 17-ketosteroids was found to be 7.4 and 10.3 mg. during two periods of 24 hours. In the latter specimen 10.1 mg. of the alpha fraction were present. Stained smears of vaginal scrapings taken at intervals showed an estrin effect but never a luteal effect.

On July 21 a left pyelolithotomy was performed. The left adrenal was found to be somewhat enlarged and about one-half of it was removed. Cut section showed the center to be thicker than normal and fat stains revealed an excessive quantity of lipoid. Within a week after operation the patient had her first menstrual period in six months. The flow lasted for seven days and was associated with cramps, suggesting that a secretory endometrium was present. An endometrial biopsy obtained one day before the next period, one month later, demonstrated a secretory endometrium. Following operation no change in the hair growth was noted, but there was a slight increase in breast development. There were 13.4 mg. of 17-ketosteroids, 10.1 in the alpha fraction, excreted on August 22, and the total excretion on August 30 was 6.8 mg. The serum sodium and potassium remained normal.

The foregoing data indicate that following the operation an improvement of the patient resulted in some respects, but there was no change in the hirsutism, the greatest concern of the patient. By this time we had some evidence that the patient was suffering from hyperadrenocorticism which presumably had resulted from the excessive production of adrenotropic hormone. Experience has illustrated that in patients with disorders of the type encountered here, neither roentgenotherapy nor surgery directed toward the adrenals or pituitary has been of much aid. Thereupon, we attempted to produce an "antihormone effect" by the prolonged administration of adrenotropic hormone. Such an approach is based on the hypothesis that injections of this hormone during a period of a few weeks would bring about changes in the body, immune or otherwise, which would prevent the adrenals from responding appreciably to either the injected hormone or the patient's own adrenotropic hormone and might thereby cause a regression of the disease. On September 3 she began receiving subcutaneous injections of adrenotropic hormone * 1 c.c. daily. Five days

* We are indebted to the Armour Laboratories, Chicago, Ill., for Adrenotropic Factor. The solution used contained 10 adrenotropic units (Collip) per 10 c.c.

later the dosage was increased to 1 c.c. twice daily, and this was continued until October 9. During the course of treatment the only clinical change observed was that the patient developed an increased desire for salt and complained of slight sensitivity to cold. On September 14 the excretion of 17-ketosteroids was 7.0 mg., 6.6 mg. of which was in the alpha fraction; October 5 the excretion was 13.3 mg. with 11.2 mg. in the alpha fraction. No change occurred in the serum sodium or potassium. At the end of the adrenotropin therapy a precipitin test was performed using the patient's serum and a specimen of the hormone used. A negative reaction was obtained even at 1:8 dilution and in spite of using a suspension of celloidin particles to increase the sensitivity of the test.

For two months after the adrenotropin therapy no treatment was given. During this time the patient's clinical status remained unchanged. The serum sodium and potassium remained normal. On October 28 a glucose-insulin tolerance test, using 65 grams of glucose, orally, and 6.5 units of insulin, intravenously, yielded evidence of insulin resistance as indicated by the following changes in blood sugar, expressed as milligrams per 100 c.c. of blood: 84, 105, 137, 151, 171, and 154, the specimens having been obtained at 0, 20, 30, 45, 60 and 120 minutes after the test was begun. Urine specimens saved over a period of four days (December 13–17) contained an average of 12.5 mg. of 17-ketosteroids per day. Thus it would seem that the adrenotropin therapy had afforded no definite benefit.

We next considered the possible effects of the administration of ovarian hormones in large doses. It has been shown [45, 46] that in rats very large doses of progesterone cause atrophy of the adrenal cortex. Certain observations have been made [47] which indicate that estrin stimulates the production of the luteinizing hormone in the pituitary gland and this substance can stimulate the adrenal cortex causing it to secrete androgenic hormone. Accentuation of this process, as by the administration of large amounts of estrogens, would tend to increase the androgenic manifestations. However, estrogens also exhibit a directly antagonistic action to therapy with androgens. Whereas it is desirable to obtain the latter effect in hirsutism the former (masculinizing) effect would, of course, be undesirable. With these principles in mind we treated our patient with a large amount of progesterone,* 25 mg. intramuscularly daily, for two months, during the last month of which 1.66 mg. of alpha estradiol benzoate was given intramuscularly three times weekly. During this therapy, in addition to studying the patient's clinical status, we also conducted balance studies, as concerned nitrogen, sodium, potassium and calcium (figure 6).

During treatment a definite enlargement of the breasts and hips resulted, but there was no change in the hirsutism. The progesterone therapy given alone or in conjunction with alpha estradiol benzoate had no definite effect on the nitrogen, sodium, potassium or calcium balances. The patient tended to remain in a slightly negative nitrogen balance. The calcium balance, although variable, tended to be negative most of the time. The serum calcium, sodium and potassium, determined twice during the course of therapy, remained normal. The excretion of 17-ketosteroids was less (average of 5.1 mg. daily for four days) at the completion of therapy than had been found at any other time. However, a determination of the 17-ketosteroids one month later showed a return to the previous high level.

During the fifteenth four-day period of the balance study the patient developed an attack of renal colic on the right, and passed a small stone in the urine. A roentgenogram of the abdomen showed several small stones in the right kidney. On March 29, 1942, the right adrenal and kidney were explored surgically. Each looked normal, but about one-third of the adrenal was removed. On microscopic examination this tissue showed many areas of tuberculosis, some of which were caseous. The

*We are very grateful to Schering Corporation, Bloomfield, N. J., for a supply of progesterone and alpha estradiol benzoate.

adrenal tissue otherwise appeared normal. A tuberculous sinus developed at the operative site and required several months to heal.

On July 17, 1942, the 17-ketosteroid excretion was 16.3 mg. It is to be emphasized that this was one of the highest values obtained in this case and was determined after the patient had been in bed several months with a chronic infection—factors which tend to lower the 17-ketosteroid excretion. On December 6 and December 30 she excreted 1.9 and 4.3 mg. of 17-ketosteroids, respectively.

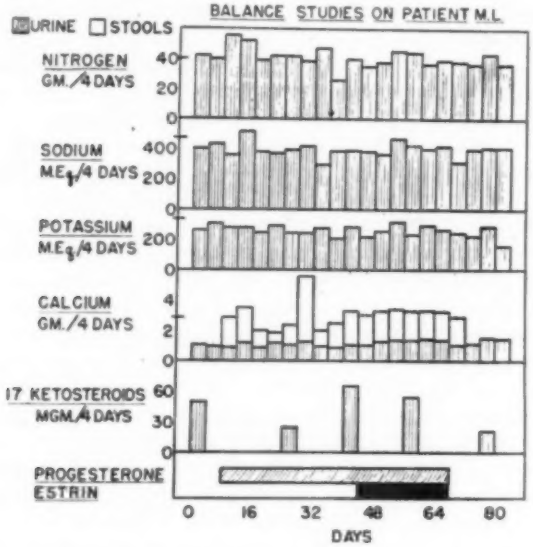

FIG. 6. (Case M. L.) Each column is for a period of 4 days. The transverse lines on the ordinate represent the content of the various substances in the diet. The progesterone was given intramuscularly in doses of 25 mg. daily. The estrin (alpha estradiol benzoate) was given, intramuscularly, in doses of 1.66 mg. three times per week.

Case 2. L. T., a 33 year old married white woman was admitted to the Fourth Surgical Service of the Boston City Hospital on April 26, 1942, complaining of right upper quadrant pain and increased hair growth on her face and body. Physical examination revealed an obese, hirsute woman with vague abdominal tenderness. Laboratory examinations were within normal limits. The 17-ketosteroid estimation was 12 mg. per 24 hours. Intravenous pyelograms showed partial fixation of the left kidney; perirenal insufflations were not conclusive but it was thought that there was enlargement of the left adrenal. She was discharged without further study.

She was admitted to the Medical Wards of the Massachusetts Memorial Hospitals on March 18, 1943, complaining of a progression of her hirsutism. She stated that she had gained 20 pounds in weight in the past three years, and had noted a definite increase in strength. Her voice had grown deep and had "cracked" several times while singing. Her skin had become increasingly greasy, acne had been present for eight or nine months, and some purplish-red striae had appeared over her arms and shoulders. Her face had become broad. Her catamenia had begun in her teens and had been regular until about one year previously. During the year preceding this hospitalization her periods were often seven to eight weeks apart and lasted for intervals varying from three to seven days.

Physical examination revealed an obese white female with a florid complexion and a prominent beard and moustache (figure 1). The temperature was 98.6° F.,

pulse 80 per minute, respiratory rate 18 per minute, and blood pressure 120 mm. Hg systolic and 92 mm. Hg diastolic. The skin was moist and pink; striae were present over the deltoid region and abdomen; acne was marked, especially on the face. The hair was increased greatly on the face, forearms, legs, and around the nipples. The pubic hair followed a male pattern. The visual fields were normal. The thyroid gland was normal in size. The heart and lungs were normal. There was slight tenderness of the right kidney where it was thought there was a palpable mass. Pelvic examination revealed normal labiae, a normal clitoris and a retroverted uterus. The neurological status was normal.

The red, white and differential blood cell counts and urinalyses were normal. The non-protein nitrogen was 22 mg. per 100 c.c. of blood; fasting blood sugar, 73 mg. per 100 c.c.; chloride, 103.4 m. eq. per liter; CO_2 combining power, 59 vols. per cent; and the creatinine was 2.1 mg. per 100 c.c. The oral glucose tolerance test yielded blood sugar values of 72, 126, 91, 66 mg. per 100 c.c., the samples having been taken at 0, 30, 60, and 120 minute intervals. The glucose-insulin tolerance test showed values of 76, 66, 86, 104 and 99 mg. per 100 c.c., the samples having been taken at 0, 30, 60, 90 and 120 minute intervals. Roentgen-rays of the skull, sella turcica, chest, and thymus were normal. Intravenous pyelograms were apparently normal. The spine showed some scoliosis in the dorsal region with slight decalcification. A 24-hour specimen of urine gave a negative assay for 10 rat units of follicle stimulating hormone. There were 12 mg. of 17-ketosteroids excreted in the urine in 24 hours. The perimetric fields were normal.

Because of the sudden progressive nature of her symptoms and the questionable enlargement of the left adrenal suggested by perirenal insufflation, the patient underwent an exploratory laparotomy on April 14, 1943. At operation, an abnormal mass was thought to exist at the upper pole of the left kidney. The right adrenal was not enlarged. Both ovaries were small and atrophic. The uterus was slightly enlarged and contained fibroids. On June 6, 1943, a left adrenalectomy was performed. Although at operation the left adrenal gland was thought to be somewhat enlarged, the pathological report was "histologically normal adrenal."

She was discharged on June 19, 1943. Soon after her operation the patient stated that she felt weaker, and also that her beard required less attention. She lost 30 pounds and her periods were reëstablished at monthly intervals. Despite her statements, we have observed no effect on her hirsutism.

Case 3. E. M.,* a 42 year old white female, was admitted to the Thorndike Ward on August 20, 1943, complaining of uncontrolled diabetes for some years, increased facial hair, and pain in the back.

Menarche occurred at 11 years and menstruation was often grossly irregular. She successfully underwent seven pregnancies, the last at the age of 32 years. Ten years previous to admission (almost immediately after her last delivery) she noted the onset of polyuria and polydipsia. At this time glycosuria was discovered. She continued to lactate for several years and noted the growth of a heavy black beard, which progressed to date and which required daily shaving. The hair of her head had thinned. The patient had been obese for about 15 years, her greatest weight being 225 pounds.

About nine years before admission she was operated upon for an ovarian cyst. She recovered successfully and was discharged on a diet and 70 units of insulin daily, which did not adequately control her diabetes. Her diabetic state remained uncontrolled despite numerous attempts to improve it.

In March, 1941, she was admitted to the Massachusetts General Hospital where it was found that she had diabetes of the insulin-resistant type, as evaluated by insulin and glucose-insulin tolerance tests. The cholesterol was 159 mg. per 100 c.c.

* We wish to thank Dr. Fuller Albright for allowing us to study this patient.

of plasma; calcium 10.8 mg. per 100 c.c. of serum; phosphorus 2.9 mg. per 100 c.c. of serum; phosphatase 2.1 Bodansky units. Roentgen-rays of the skull and spine demonstrated mild osteoporosis. The sella turcica was normal. A perirenal air insufflation was thought to show a suspicious shadow in the region of the right adrenal. The 17-ketosteroid assays were 25.6 and 24.3 mg. per 24 hours. The patient was given a ketogenic diet, without insulin (although she had been taking 70 units previous to admission). She did not develop ketosis and noted no subjective change except increased weakness. When she was given a normal diet she felt better but there were no appreciable changes in her blood or urinary findings.

In June, 1941, she was admitted to the Massachusetts Memorial Hospitals complaining of headaches. Her blood pressure was 142 mm. Hg systolic and 100 mm. Hg diastolic. A lumbar puncture, performed to relieve the headaches, showed an initial pressure of 220 mm. of water (although the patient possibly was not relaxed). An intravenous pyelogram was interpreted as showing an enlarged left kidney. The 17-ketosteroid excretion was 18 and 14.4 mg. per 24 hours respectively, on two occasions. She was discharged on a diet of carbohydrate 150 grams, protein 70 grams, fat 60 grams, and was told to take 45 units of protamine insulin daily. A later course of roentgen-ray therapy directed to the pituitary had little apparent effect on her diabetes.

Physical examination revealed a middle-aged woman with plethoric features and marked girdle obesity (figure 7). The blood pressure was 140 mm. Hg systolic and 90 mm. Hg diastolic. Black hair was present in increased amounts on the upper lip, chin, arms, legs, and abdomen, the latter having a male pattern. The skin was thin, reddish-purple striae were present over the shoulders and hips, and the superficial veins were prominent. There were one or two (spontaneous) bruises on her lower extremities. The thyroid was palpable and there was a firm nodule to the right of the isthmus. The lungs and heart were normal. The abdomen presented a large panniculus of fat; no internal organs or masses were palpable. Pelvic examination revealed hypertrophy of the major and minor labiae, and a clitoris about twice the normal size. Neurological examination was normal.

Blood cell counts were normal. Repeated urinalyses showed a 4 plus sugar reaction. Fasting blood sugars varied from 180 to 252 mg. per 100 c.c. There were 95 m. eq. of chloride per liter of serum; total protein, 6.9 grams per 100 c.c. of serum. The glucose and insulin tolerance test gave the following values: 204, 222, 270, 292, and 345 mg. of sugar per 100 c.c. of blood, the samples having been taken at 0, 30, 60, 90 and 120 minutes respectively. Two determinations of the basal metabolic rate were within the normal range. Roentgen-rays of the sella turcica and intravenous pyelograms were normal.

The patient was given a constant diet of protein 71, carbohydrate 162, fat 58, without insulin. On this regimen she excreted varying amounts of sugar in the urine, ranging from 42 to 66 grams per 24 hours. She did not show a negative nitrogen balance. After she had been maintained on the above diet for a control period of 16 days, she was given thiouracil 0.6 gram per day from September 1 to 12; 1 gram per day from September 13 to 21. She displayed mild ketonuria during the last week of treatment. Results of this therapy are discussed separately.

On September 8, 1942, she was discharged on her previous diet of carbohydrate 150, protein 70, fat 60, and was told to take 24 units of protamine insulin daily before breakfast. She has been taking thiouracil 0.2 gram daily for eight months but has noted no change in her hirsutism.

Discussion. These three patients present certain of the manifestations of Cushing's and of the adrenogenital syndrome.

The first patient (M. L.) is a good example of the adrenogenital syndrome coming on after menarche. The excellent musculature, clitoral enlargement, masculinization and somewhat elevated 17-ketosteroid excretion are characteristic. The distribution of fat, and tendency toward insulin resistance are more commonly associated with Cushing's syndrome, however.

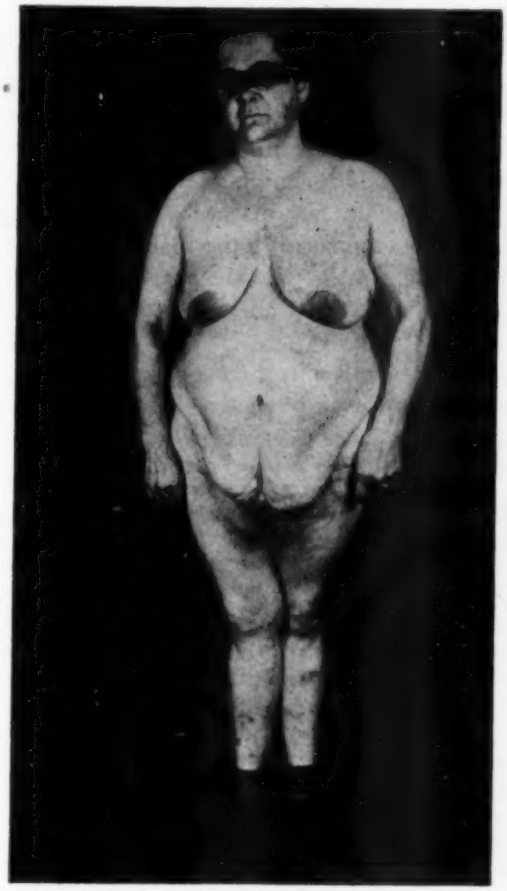

FIG. 7. (Case E. M.) Note the obesity of the trunk contrasted with slim extremities. Hair and veins are prominent over the breasts. Legs show spontaneous bruises. Beard is not prominent, since patient had just shaved.

The slightly negative nitrogen balance may be related to the concomitant presence of chronic infection.

The second case (L. T.) is probably an example of the same disease in an older woman. This patient differs, however, in that she had much more acne, a normal clitoris, a normal glucose and insulin tolerance test and low 17-ketosteroid excretion.

It is quite evident that some functional alteration in physiology has occurred in both these patients. Neither had any clinical evidence of a pit-

uitary lesion. In both the ovaries were ruled out as a cause of the patient's trouble. Surgical exploration showed some hypertrophy of one adrenal in the first patient. The ablated adrenal of the second patient was normal.

These patients demonstrate the inadequate correlation between morphology and function. Certainly the severity and progression of these patients' symptoms is eloquent evidence of malfunction. Yet the histological evidence of adrenal hyperfunction was slight in one and absent in the other. Even so, the positive morphological findings in one of these "idiopathic" cases suggest that, with the coming of improved histological technics, many cases will be removed from this classification.

The third patient apparently fulfills the criteria for a diagnosis of Cushing's syndrome. Yet here again we could not localize the primary anatomical etiologic factor in her disease. Recently another such patient has been reported,[48] again emphasizing the inadequacy of our diagnostic aids. Together, these three cases also provide all the comment necessary on the ineffectuality of surgery, roentgen and medical therapy on the progress of the hirsutism.

Hirsutism Associated with Pituitary Disease—Acromegaly. Hirsutism is sometimes associated with acromegaly. One such case was observed in our group. Because this patient came to autopsy we include her clinical history and postmortem findings.

Case 4. M. D., a 50-year old white unmarried female, was admitted to the Second Medical Service of the Boston City Hospital, on July 11, 1941, in marked cardiac failure. Twenty years previous to her admission her features grew coarse, her hands enlarged, her voice deepened, and headaches began to accompany her menses. Seventeen years before admission she underwent a leiomyomectomy, followed by amenorrhea, which persisted until two years previous to admission, when she had several normal catameniae. Amenorrhea then recurred. Sixteen years prior to the present entry, she developed diabetes mellitus and thyrotoxicosis. An adenomatous colloid goiter was removed. Six years later, hirsutism developed. During the four years preceding admission, fasting blood sugars ranged from 178 to 322 mg. per 100 c.c. and blood pressures from 210 mm. Hg systolic and 110 mm. Hg diastolic to 140 mm. Hg systolic and 80 mm. Hg diastolic.

Physical examination revealed an orthopneic, well-nourished, middle-aged woman with acromegalic features. The upper lip and jaw were very hairy. The skin was thick and coarse. The hands and feet were large. The temperature was 98° F.; pulse 100; respiratory rate 30 per minute; and blood pressure 148 mm. Hg systolic and 112 mm. Hg diastolic. A thyroidectomy scar was present, and an increased amount of adenomatous thyroid tissue was palpated. The lungs revealed dullness and moist râles at the left base posteriorly. The heart was enlarged, and there was a systolic murmur at the apex. The liver was enlarged and tender. The pubic hair had a male pattern, but there was no hypertrophy of the clitoris. There was extensive pitting edema of the ankles, legs, and sacrum. The neurological examination was normal.

Laboratory tests revealed the following: Blood cell counts were normal. Numerous urines showed 1 plus to 4 plus albumin, and no sugar. The blood Hinton reaction was negative. The non-protein nitrogen was 25 mg. per 100 c.c.; chlorides 100 m. eq. per liter; cholesterol 250 mg. per 100 c.c.; calcium 10 mg. per 100 c.c. of

serum; phosphorus 3.9 mg. per 100 c.c. of serum; phosphatase 4.5 Bodansky units; total protein 5 grams per 100 c.c. Numerous fasting blood sugars were less than 120 mg. per 100 c.c., with one exception which was 175 mg. per 100 c.c. The roentgen-ray of the skull was interpreted as showing Paget's disease; roentgen-rays of the hands showed elongation of the first metacarpals. The basal metabolism was minus 12 per cent (after partial recovery from cardiac failure). The follicle stimulating hormone assay was positive for 18 rat units. The 17-ketosteroid excretion was 4 mg. per 24 hours. A glucose-insulin tolerance test showed values of 107, 144, 179, 175, 222 mg. per 100 c.c., specimens having been taken at 0, 30, 60, 90, and 120 minute intervals.

The patient's cardiac failure improved. She was given desiccated thyroid (U.S.P.) .06 gram per day and showed further improvement.

On September 23, 1941, the patient reëntered the hospital, with a recurrence of her congestive failure. She failed to respond to therapy and died.

Postmortem Examination: The external appearance was that already noted in the antemortem examination. The liver was slightly enlarged (2,480 gm.) extending 4 cm. below the costal margin. The spleen (320 gm.) showed a small area of infarction. The pleural cavity had many adhesions on the right, with a small quantity of serous fluid in the right base. The heart (620 gm.) showed hypertrophy of both ventricles and considerable dilatation of the right auricle. Both coronary arteries were atheromatous. An adherent, pale-gray thrombus was present over both surfaces of the anterior half of the interventricular septum.

The examination of the endocrine organs was as follows:

Pituitary. The organ weighed 1 gram. The anterior lobe contained a soft necrotic area, which comprised one-third of its bulk. Histologically it was found that much of the anterior lobe consisted of a pituitary eosinophilic adenoma largely destroyed by a recent infarct. The cells of the remaining portion of the gland showed a predominance of basophiles.

Thyroid. The lateral lobes were of usual size, and contained numerous cysts and much fibrous tissue. Microscopically there was great variation in the size of the follicles, most of which were filled with old colloid. There was no epithelial hyperplasia.

Adrenals. The right adrenal weighed 16 gm., the left 12 gm. They were firm, and there was a very deep yellow color of the cortex. Histologically there was no hyperplasia of the cortices.

Genital organs. The uterus was small and firm, displaying an inactive endometrium. The *ovaries* were small (5 cm. in diameter). No follicles were seen.

The *pancreas* and *parathyroids* were not grossly or histologically remarkable.

Discussion. This patient's clinical history suggests that 25 years previous to our observation, she began to develop her pituitary tumor. The headaches at this time were probably due to enlargement of the neoplasm. In response to increased growth hormone production, her features grew coarse, and her hands and feet enlarged. A few years later, presumably as a response to increased thyrotropic and pancreatropic stimulation she developed hyperthyroidism and diabetes mellitus. As evidence of probable adrenal stimulation are the hirsutism and amenorrhea. About two years before her final admission, some reverse of a previously progressive process seems to have occurred. This was not brought about by the infarct found at postmortem examination, however, since the latter was of more recent occurrence. She had the onset of myxedematous symptoms, concurrent im-

provement of her diabetes and occasional menses. Despite improvement in most of her findings the hirsutism did not disappear. It is also interesting that the case shows marked secondary adrenal hypertrophy which probably explains the persistence of facial hair. A similar case of acromegaly reported by Kennedy (quoted by Schwartz [24]) underwent a post-hypophysectomy remission of all symptoms save the hirsutism. The low 17-ketosteroid excretion in this patient was probably due to poor clinical status.

We have been impressed by the number of our "idiopathic" cases who presented suggestive acromegaloid features. Half the group gave a history of increased growth and strength over that of similarly aged companions in their early life. Although most of the women were not tall, many had broad faces, heavy brows, prognathous jaws, large hands and stubby fingers, all suggestive of acromegaly. Four of these patients had goiters and one had suffered from thyrotoxicosis in the past. Two gave a history of persistent lactation for a long period of time. One patient had hyperplasia of the gums similar to the "partial acromegaly" described by Zondek.[49] This may be merely a congenital characteristic, however, since it has occurred in other members of her family.

Hirsutism Associated with Adrenal Disease—Pseudohermaphroditism. According to the most accepted concepts, the pseudohermaphrodite represents virilization due to adrenal hyperfunction. We have observed one such case which exhibited "hirsutism" as a precocious appearance of abundant axillary and pubic hair. The face was not involved (figure 8).

Case 5. B.M.,* an eight year old white girl, was admitted to the Massachusetts Memorial Hospitals September 21, 1943. Her birth history was normal. At the age of one year, a doctor had noted unusual clitoral enlargement and had advised investigation. The family noted progressive enlargement of the organ but deferred treatment. The patient had always exhibited thoroughly feminine habits and was unaware of her abnormality. The family history was irrelevant.

The physical examination revealed a shy, feminine-acting girl, with a very deep masculine voice. She was slender and her body habitus was masculine. She was the size of a 12 year old girl, weighing 91 pounds and measuring 57 inches in height. Her strength was distinctly better than normal. The blood pressure was 150 mm. Hg systolic and 70 mm. Hg diastolic. She had considerable facial acne. The skin was seborrheic. The pubic and axillary hair was well developed. The thyroid was not enlarged. The heart and lungs were normal. No abdominal masses could be palpated. Pelvic examination revealed well developed labiae majorae covered with abundant hair. The clitoris was a large, penis-like structure, three inches in length, with a well-developed glans (figure 9). On the inferior surface a frenulum was present, running back into the vestibule. On the inferior aspect of the frenulum were several openings, one of which proved to be the urinary meatus. Cystoscopic examination revealed a normal bladder. The vagina was well-developed.

Laboratory studies revealed the following: Red, white, and differential blood cell counts and urinalyses were normal. The basal metabolic rate was plus 2 per cent. The fasting blood sugar was 94 mg. per 100 c.c.; total protein 7.0 grams per 100 c.c. of plasma; calcium 10.9 mg. per 100 c.c. of serum; phosphorus 3.8 mg. per 100 c.c. of

*We wish to thank Dr. Samuel Vose for allowing us to study this patient.

serum; alkaline phosphatase 11.4 Bodansky units; sodium 336 mg. per 100 c.c. of serum. The glucose tolerance test gave the following values: 125, 89, 100, and 60 mg. per 100 c.c., the samples having been taken at 0, 30, 60 and 120 minutes. The insulin tolerance test gave values of 111, 80, 85 and 90 mg. per 100 c.c., the samples having been taken as above. Intravenous pyelograms were normal. The sella turcica was

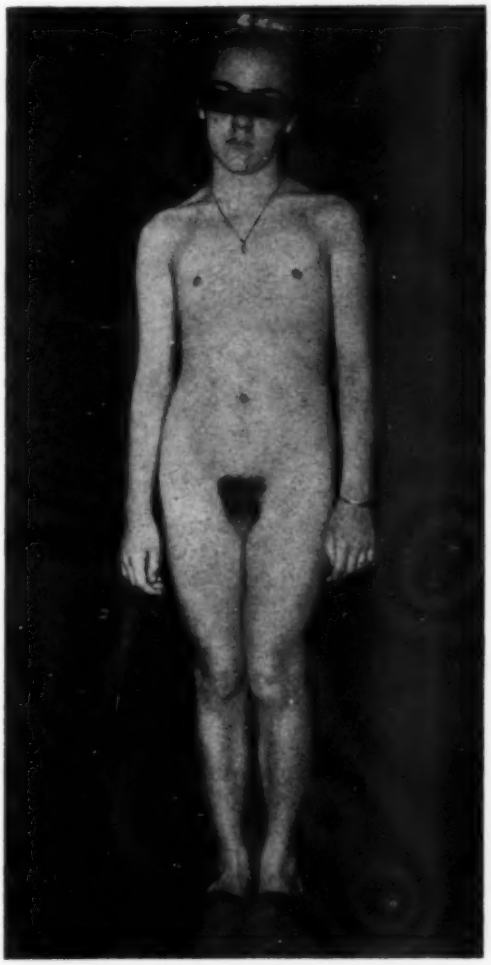

FIG. 8. (Case B. McI.) Age 8 years. Note the boyish figure and good musculature.

normal. Roentgen-rays of the long bones and epiphyses showed development consistent with that of a 14 year old girl. There were 8.4 and 14.1 mg. of 17-ketosteroids excreted per 24 hours in two samples assayed.

On October 8, 1943, an exploratory laparotomy was performed. The uterus, tubes, and ovaries were normal. Both adrenals were palpated, and the right was thought to be enlarged. On November 26, 1943, through a right lumbar incision, the right adrenal gland was found to be "larger than an adult's adrenal gland." A resection of one-half of the gland was performed, since the size of the other gland was

unknown. Histological examination of the resected adrenal revealed cortical hyperplasia.

Six months following the operation the patient's voice was of higher pitch although still resembling that of a boy. Acne was much improved. There was some increased areolar pigment and beginning mammary development. The genitals were unchanged. The laboratory studies were essentially unchanged. The 17-ketosteroid excretion, however, had dropped to 3.8 and 4.4 mg. per 24 hours, in two samples analyzed.

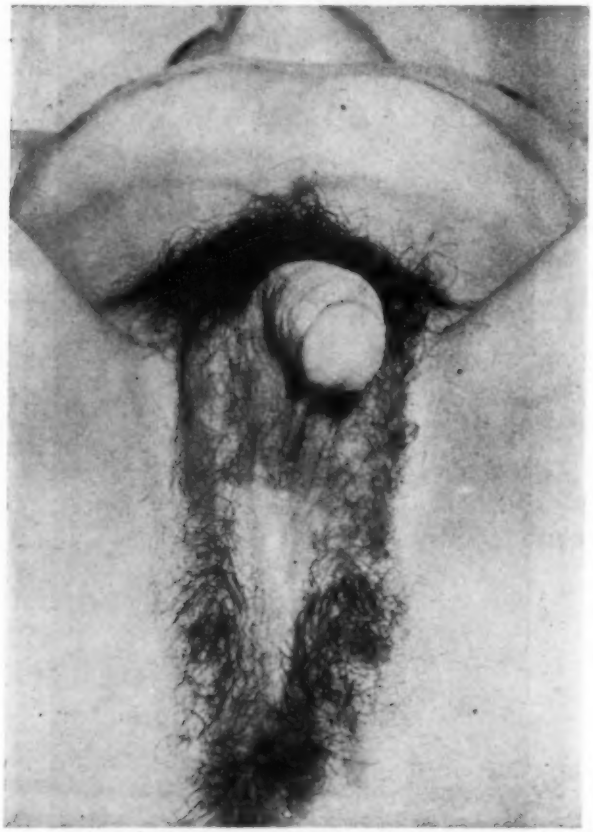

FIG. 9. External genitals of Case B. McI. The clitoris was about 3 to 4 inches long. The urethra was one of the multiple openings in the frenulum. Vagina about normal size.

Comment. This patient is a classical example of pseudohermaphroditism, presumably resulting from adrenal cortical hyperplasia. Actually, it is the adrenogenital syndrome, beginning in embryonic life. The body cells are in the process of differentiation and the effects of increased androgen production are marked. The causative etiological lesion may be an adrenal tumor, adrenal hyperplasia, or a hyperfunction of some androgenic adrenal component (such as the X-zone).[50]

The effects of operation on the appearance of this girl are marked. There has been a definite diminution in androgenic influences as demonstrated

by the beginning breast development, increase in vocal pitch, and lessened acne. The drop in the 17-ketosteroid excretion is a good chemical indication that there has been a diminution of the androgenic function of the adrenal. The genital malformation will undoubtedly require plastic surgery.

Transient Hirsutism, Associated with Pregnancy.

A. C.,* aged 28, a white primagravida, was admitted to the Boston Lying-In Out-Patient Department on September 19, 1941. The patient stated that her last menstrual period had occurred on July 23, 1941. In September, 1941, she first noted the appearance of rapidly growing blackish hair on her malar eminences, ear lobes, eyebrows and upper lip. By October, 1941, her chin, mammary areolae, arms and legs were involved. She had always had a male pubic hair distribution, but this had increased. The patient was not at all perturbed over her hirsutism, since her mother also had been hirsute during pregnancy, and had lost all the abnormal hair post partum.

Past history revealed that she had always been a "big girl." At 11 years she had weighed 125 pounds. Her catamenia began at 11 years, had occurred every 28 days, for a five-day period. Her first menses were associated with nausea, vomiting and dysmenorrhea.

Physical examination revealed an obese young woman with marked hirsutism. The temperature was 98.6° F., pulse 90, respiratory rate 20 per minute, weight 179 pounds and height 67 inches. The blood pressure was 125 mm. Hg systolic and 75 mm. Hg diastolic. Coarse black hair covered her upper lip, cheeks, chin and jaw, and grew out of her ears and ear lobes. There was increased hair on the legs and forearms, and a pronounced male pubic hair growth was present. The areolae of the nipples were surrounded by ten or twelve long dark hairs. The thyroid was diffusely enlarged. The clitoris was slightly hypertrophied. Pelvic findings were consistent with pregnancy of three months' duration. Otherwise, the physical examination was normal.

Roentgen-rays of the sella turcica were normal. The basal metabolic rate was minus 10 per cent. The 17-ketosteroid excretion was successively 15.04 and 13.92 mg. per 24 hours (December, 1941).

The hirsutism continued to increase until February, 1942. Spontaneous depilitation then occurred beginning about the ears and right side of the face. Later the hair on the abdomen and large patches on the thighs were denuded. The clitoris remained enlarged. In February, 1942, the patient had some vaginal bleeding which stopped spontaneously.

The patient went into a 20-hour labor on May 13, 1942. She had some uterine inertia and was delivered with low forceps. The child was given early formula feedings because of oligogalactia. The hirsutism was still present at delivery but disappeared entirely post partum.

Comment. It is known that the adrenal enlarges in animals during pregnancy.[11] The hirsutism seen in human females during gestation is due presumably to similar adrenal hyperfunction. The fact that relatively few patients suffer from transient hirsutism of pregnancy suggests that other factors are also implicated. This patient had a familial history of hirsutism which suggests that genetic factors are involved. This case has several other points of interest. Although she was not hirsute previous to her

* We wish to thank Dr. David Hurwitz for furnishing the information regarding this patient.

pregnancy, her "bigness," obesity, and male hair distribution are reminiscent of our "idiopathic" hirsute group. Whether the clitoris was enlarged before her pregnancy or as a result of it cannot be stated. The threatened abortion, uterine inertia, and oligogalactia also seem to indicate some lowering of typical feminine function, possibly due to androgenic influences. The beginning depilitation before the delivery of this patient is difficult to explain. However, it has been shown [51] that estrogen excretion increases about the sixth month of pregnancy. It was at this time that the patient began to lose her hirsutism. With the increase in estrogens we might postulate that the estrogenic-androgenic ratio reached a better balance and the hirsutism diminished as a result.

Another patient with transient facial hirsutism of pregnancy whom we have seen did not lose her abnormal hair until after delivery. This individual was slender and had no family history of hirsutes. The 17-ketosteroid excretion ranged from 1.6 to 3.2 mg. per 24 hours on three occasions. The values are actually lower than normal.

Therapy. The treatment of hirsutism is grossly unsatisfactory. Most patients attempt a purely local remedy by shaving, tweezing, depilitation and electrolysis, all of which are temporary and annoying. As has been pointed out in a recent editorial, the more severe the cause of hirsutism the more likely the cure.[52]

There is general agreement that when the cause is a tumor, surgical removal is indicated. The results are often brilliant, with a complete reëstablishment of all feminine functions and characteristics. However, even here the hirsutism may persist.[53] Also, in the case of adrenal tumors, the opposite gland may be secondarily atrophied and unable to maintain life function.[31] When the cause is a basophilic tumor of the pituitary, either surgical or roentgenological treatment is generally unsatisfactory. In the case of adrenal hypertrophy, resection of the cortex and unilateral adrenalectomy have caused only slight transient improvement in most cases. This certainly was our experience in two cases (M. L. and L. T.).

Androgens and estrogens are produced by both males and females. Although it is often difficult or impossible actually to demonstrate increased androgen production in hirsutism, it is frequently assumed that imbalance in the androgen-estrogen ratio exists. It would seem that hormonal therapy might thus cause disappearance of masculinization.

Synthetic and natural estrogens have been tried, although results have not been encouraging. We have given synthetic estrogens (diethylstilbestrol) to the two post-menopausal cases in 1 to 2 mg. daily doses for eight months without effect on the hirsutism. In six other cases (R. M., M. L., M. F., F. M., K. C., S. D.) both synthetic and natural estrogens given in adequate doses for similar periods of time had no effect on the hirsutism. One patient (R. M.) had definite increase in her acne during therapy with stilbestrol. It is of passing interest to note that estrogens cause adrenal hyper-

trophy in animals and presumably have the same effect in man, as suggested by the growth of pubic and axillary hair in hypo-ovarian dwarfs under estrin therapy.[9] Thus it would seem that estrogens might possibly enhance the condition already present.

Progesterone, in large doses, is reported to cause adrenal atrophy.[45, 46] This is apparently mediated through the inhibition of luteinizing hormone of the pituitary, which is thought to stimulate the adrenal cortex.[47] One attempt to diminish adrenal function by this means (M. L.) was an apparent failure. In three patients, we successfully reëstablished normal catamenia by the concomitant use of estrogens and progesterone. Even after menstruation occurs in a normal fashion for several months, the hirsutism persists. Simple reduction of weight has had no effect on the hirsutism. In four patients the effect of the new antithyroid drug 2-thiouracil, introduced by Astwood,[54] has been noted. In the course of study it was noted that large amounts of thiouracil were taken up by the adrenals of both animals and man.[55] We also observed that an occasional hyperthyroid patient treated with this drug exhibited chloride retention, depression of CO_2 combining power and slight edema.[56, 57] Since these patients had no evidence of renal or cardiac disease, and had normal serum proteins, we thought that this effect was possibly mediated through the adrenals.

Each of the patients was first brought into the hospital and a balance study performed, to determine the effects of thiouracil administration on nitrogen and electrolyte balance. Slight retention of nitrogen, sodium, chloride, creatine and creatinine was noted. A full report of these results is to be found elsewhere.[57] The glucose and insulin tolerance tests and 17-ketosteroid excretion were not affected. The four patients have been maintained on thiouracil * in doses of 0.2 to 0.4 gram daily for 10 months. Two of the patients who have diabetes mellitus have discontinued insulin and have remained without sugar in the urine while on therapy. This is probably not a direct result of drug therapy but due to the fact that they have lost some weight and have been following their diet more strictly.

One woman (G. K.) whose hair was quite gray now has a definite admixture of yellow. She has seen no change in the character or growth of her facial hair, although it is now removed with greater ease. After eight months of therapy (0.4 gram daily) the drug was discontinued in this patient, due to the onset of symptoms of myxedema and depression in her basal metabolic rate.

Two other patients (L. M. and K. McG.) state that they do not shave as frequently as before the treatment, although we can note little change. The fourth woman (E. M.) has observed no effect of thiouracil on her diabetes or facial hirsutism. The abnormal distribution of body hair has not been affected.

* We wish to thank the Lederle Company, Pearl River, New York, for the thiouracil (Deracil) used.

Discussion

A purely clinical differentiation of hirsutism is often difficult because it occurs in so many different conditions. It is important to note that the length of time since the onset of symptoms is often of great value in excluding a malignant process. Although the severity of masculinization is often suggested to differentiate the "idiopathic" variety from pituitary, adrenal and ovarian types of hirsutism, our series would not bear out this fact. Likewise, patterns of fat distribution, the quality and location of the abnormal hair produced, and the presence or absence of clitoral hypertrophy, although formerly considered to be of great significance, are of little practical use in differentiating among the various lesions.

Pituitary lesions have as their most valuable diagnostic aids the finding of an enlarged sella turcica by roentgen-ray, or a defect on the visual field by perimetry. Symptoms relative to increased intracranial pressure, or cerebral irritation may occasionally be helpful. The physical and metabolic changes once thought typical of pituitary basophilism may occur with adrenal cortical lesions.

In diagnosing adrenal lesions, the palpation of an abdominal mass is most helpful. Careful studies of the kidney-adrenal area with pyelograms, and possibly perirenal air injections, may yield valuable confirmatory information.[58] Great increases in 17-ketosteroid excretion, especially of the beta and non-alcoholic fractions, are valuable in diagnosing cases of adrenal carcinomata.[42, 43] Lesser increases in total 17-ketosteroid output occur in some instances of "hyperplasia."

Arrhenoblastomata of the ovary are not usually associated with hypertension, disordered carbohydrate metabolism, osteoporosis or polycythemia. It has been stated that the presence of a pelvic mass, when associated with hirsutism, an enlarged clitoris and normal excretion of 17-ketosteroids, should make one suspicious of an ovarian tumor.[43] We have seen one patient (S. W.) who had severe virilization, an enlarged clitoris, low 17-ketosteroid assays and a pelvic mass, whose ovarian "tumor" proved to be a tubo-ovarian abscess at operation. Similar findings may also occur with diffuse luteinization of the ovaries.[23] If, after careful search, ovarian, pituitary or adrenal causes are ruled out, the case then becomes one of "idiopathic" hirsutism.

The relationship between heterosexual hypertrichosis and certain instances of adrenal hyperfunction has been quite well established. This is most clearly acceptable with the demonstration of an adrenal lesion per se. In the case of pituitary tumors associated with hirsutism, adrenal hypertrophy is often demonstrable, and the mechanism seems adequately explained by an excessive stimulation of the adrenal cortex by pituitary adrenotropins. Ovarian tumors associated with masculinization presumably produce substances similar in action to the cortical steroids. There are also rare masculinizing ovarian tumors actually composed of functioning adrenal cortical

cells.[19] When none of these explanations obtains the case becomes "idiopathic." This is always an unsatisfactory diagnosis and especially so when we realize that most hairy women fall into this classification. At present the cause of this condition is generally thought to reside in an inherent, constitutional defect in the hair follicles themselves, influenced perhaps by racial or familial genetic factors. Although the hereditary tendency toward hairiness is probably present in many individuals, we believe that the clinical similarity of many of these idiopathic cases, to those associated with either primary or secondary hyperfunction of the adrenal cortex, is suggestive. Although 17-ketosteroid determinations are often normal or even subnormal, some cases of "idiopathic" hirsutism have been found associated with increased titers [59] of androgens, or to have increases in the excretion of androgens in relation to estrogens.[60] This seems further to suggest adrenal cortical hyperfunction. At present the pathologist can give little help in the situation because of current lack of methods adequate to demonstrate altered function in cells which may look anatomically normal under the usual stains.

We feel that with the development of better histochemical technics, more generally applicable methods of specific steroid assay and more sensitive tests of adrenal cortical function than now exist, many cases of "idiopathic" hirsutism will be reassigned to a more proper category. Also, we feel that further knowledge of the enzyme systems involved in adrenal physiology may point the way toward a more rational therapeutic attack on hirsutism.

Summary

Normal human hair production is apparently the result of (a) inherent qualities within each hair follicle, and (b) endocrine influences. The effects of hormonal control on hair growth are especially apparent in diseases affecting the adrenals, anterior pituitary, thyroid, and gonads. Hirsutism in females is often associated with anterior pituitary, adrenal cortical and ovarian disease, especially of a neoplastic character. The majority of hirsute women, however, demonstrate no gross endocrine abnormality and are classed as examples of "idiopathic" hirsutism.

Twenty-nine cases of "idiopathic" hirsutism have been studied in some detail. Twenty-four of the cases had heavy beards requiring daily shaving; 23 had the male type of pubic hair distribution. Clitoral enlargement was present in 11 cases. Thirteen had menstrual abnormalities. Obesity was present in the majority. Glucose-insulin tolerance tests were abnormal in 19 cases, suggesting the possibility of an insulin resistant type of carbohydrate defect. The 17-ketosteroid excretion was normal or subnormal in the majority of the group. Case histories of three patients, including a metabolic balance study of one, are given.

One case of hirsutism associated with acromegaly has been reviewed, with autopsy findings.

One case of pseudohermaphroditism is recorded in detail.

Two cases of transient hirsutism of pregnancy were studied. One case is reported in detail.

The therapy of hirsutism is generally unsatisfactory. In our series, both hormonal and operative measures were employed without success. Four cases were treated with thiouracil in doses from 0.2 to 0.4 gram daily for eight months. The results were not encouraging.

The differential diagnosis of hirsutism is briefly discussed. It is felt that with increased knowledge of histochemical technics, steroid chemistry and enzymology, many cases of "idiopathic" hirsutism will be found to have evidence of hyperadrenocorticism.

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PENICILLIN TREATMENT OF SULFA-RESISTANT GONORRHEA; RESULTS OF 500 CASES TREATED WITH 50,000 UNITS OF PENICILLIN *

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During the early observation of the effects of penicillin on various organisms the gonococcus was found to be susceptible, and during 1943 its successful use in several small series of cases was reported.[1, 2, 3] Recently Ferguson and Buckholtz,[4] in reporting the results of treatment in 735 cases of sulfonamide resistant gonorrhea with varying doses of penicillin, indicated that a dosage of at least 100,000 Oxford units was necessary for uniformly satisfactory results. During the summer of 1943 O'Reilly General Hospital, among a number of other general hospitals, was assigned the task of treating several groups of sulfa-resistant gonorrhea with varying doses of penicillin. Following this experimental period, the Office of The Surgeon General, in September 1943, advised that the dosage be established at 50,000 Oxford units as an initial course, with 100,000 Oxford units to be used subsequently in the event of failure to obtain adequate response to the initial therapy. When a case failed to respond to the second course of penicillin, the treatment was to be considered a failure and other means of therapy were to be initiated. The results of such treatment in 500 consecutive cases of sulfa-resistant gonorrhea form the basis of this report.

Approximately 90 per cent of these cases were received as transfers from various station Hospitals of the Service Command where they had failed to respond to the administration of sulfonamides. The remainder were received as casuals or admitted from the local command, and had ineffectually received sulfonamide therapy under our care. In all cases treated with penicillin the urethral discharge had persisted and cultures were positive for *N. gonococcus* at least three days following the discontinuance of two courses of sulfonamide, each course consisting of at least 20 grams of sulfathiazole or sulfadiazine over a five-day period.

Administration of the Drug

Penicillin powder was dissolved in sufficient sterile, distilled water so that 2 c.c. contained 10,000 Oxford units and was routinely administered intramuscularly. Care was maintained to group the cases so that freshly prepared solutions were always used. The original course of 50,000 Oxford units was given in doses of 10,000 Oxford units every three hours for five doses.

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From the Medical Service, O'Reilly General Hospital.

Where it was necessary to administer 100,000 Oxford units, injections of 10,000 Oxford units were given at hourly intervals for 10 doses. During the first few weeks of our program the patients were required to remain in bed five days following penicillin therapy. Later the patients remained in bed only on the day they received penicillin and this was done chiefly for the purpose of convenience in administration. No other specific measures were carried out and the patients partook of food and fluids as desired. There were no serious reactions to the drug. Most of the patients admitted to having slight burning sensations deep in the muscles for no longer than a few hours but this was never severe and in no cases was it necessary to use other than the gluteal regions for injections. A temperature of 99° to 100° F. on the day of injection was common. One patient experienced an elevation to 104° F., but this was probably due to a flare-up of an accompanying acute balanitis. Generalized urticaria followed the injection of penicillin in five instances. The longest duration of the urticaria was five days. Several days following the disappearance of the urticaria each of these cases was given 0.1 c.c. of dilute penicillin solution intradermally and in no instance was there any skin reaction observed. In none of these cases was a second dose of the drug necessary so that the effect of a repeated intramuscular injection was not observed.

Criteria for Cure

During the early experimental use of penicillin our cases were followed over a period of 21 days subsequent to therapy. Material obtained by prostatic massage and centrifuged urine sediment at 48 hours, 7 days, 14 days, and 21 days was cultured by the Laboratory Service on chocolate blood agar plates containing proteose No. 3 peptone and yeast extract and was cultured for 48 hours at 37° F. in a 10 per cent CO_2 atmosphere. No case was pronounced cured if any of these cultures were reported to be positive for *N. gonococcus*. It was found that in most instances when the cultures taken at 48 hours and at seven days following therapy were negative the subsequent cultures were also negative, but in a few instances a positive culture was found for the first time after therapy on the fourteenth or twenty-first day.

Later in the course of this study all cases were observed over a period of seven days, or longer if clinically indicated, before discharge to duty or institution of further therapy. In all cases in which material could be obtained by stripping the urethra, cultures were obtained 48 hours and seven days following therapy. If no material could be obtained from the urethra or if cultures or smears on available serous discharge were negative at the end of seven days, the case was considered to be cured of gonorrhea.

In all cases returned to duty from the local command an inspection for urethral discharge was required at weekly intervals until three weeks had elapsed following therapy. As previously noted, over 90 per cent of all

cases were received from other commands and were returned to their organization on discharge from this hospital. In such cases the soldier was instructed to report to his medical officer and a form letter requesting examination of the soldier at weekly intervals for three weeks was forwarded to his organization commander. This letter was to be returned to us with a statement by the organization surgeon as to the results of his examination. Responses to this follow-up letter were received in only about 50 per cent of the cases. Admittedly, it is more than possible that some cases which relapsed following discharge from this hospital were never reported to us or returned to us for treatment. However, after due consideration, we feel that the number of such cases which were not reported would be small and would not affect our statistics to any great extent. Actually, only six cases were returned to us for treatment after what was considered a relapse of symptoms.

Results

Almost without exception, in those who responded to therapy, there was a remarkable decrease in the symptoms of burning and frequency and in the amount of urethral discharge within a period of six hours following the first injection of penicillin. By the next day the urethral discharge was usually scanty and serous in character. At the end of 48 hours the discharge had almost ceased and 456 cases had negative cultures at that time. However, 18 of these cases subsequently showed a positive smear or culture for *N. gonococcus* and only 438, or 87.6 per cent, were finally considered cured by one course of 50,000 Oxford units.

The 62 cases that did not respond favorably to the first course of 50,000 Oxford units of penicillin were given a second course of 100,000 Oxford units. Following this dose 45 cases became culturally negative for *N. gonococcus* and symptom free. However, a urethral discharge and positive culture persisted in 17 cases. After additional injections of penicillin to a total of 350,000 Oxford units and local therapy all cases became culturally negative for *N. gonococcus* and three became asymptomatic. Fourteen cases continued to have a urethral discharge due to secondary infection.

An attempt was made to determine whether the cases which failed to respond to penicillin harbored a penicillin-resistant strain of *N. gonococcus*. The organisms found in 30 unselected cases were tested for penicillin sensitivity as compared to a standard Oxford strain of *Staphylococcus aureus* whose growth was inhibited by .05–.03 Oxford units of penicillin and considered "sensitive." In the *N. gonococcus* organisms tested for sensitivity, all were inhibited in a range of from .05 to .005 unit and were considered "sensitive" to "very sensitive." Of these 30 cases tested, six failed to respond to the injection of 50,000 Oxford units and two cases were failures after an additional 100,000 Oxford units. No relationship to the penicillin sensitivity of the organisms involved in these cases could be demonstrated.

Complications of Gonorrhea

Gonorrheal arthritis was the most debilitating and serious complication encountered and was seen in eight cases. As far as could be determined, the course of this complication was not as favorably influenced by penicillin as other similar cases treated with sulfonamides have been. In all eight cases of gonorrheal arthritis, the accompanying urethritis was apparently cured. Acute epididymitis was seen in 15 cases. It was not thought that the course of this complication was shortened by penicillin and usually required 14 to 21 days before subsidence of symptoms.

Cases of long standing gonorrheal urethritis presented the most difficult problem in this series of cases. Seventeen of our cases fell into this group, all having had intermittent or persistent urethral discharge for a period of from one to 15 years, complicated by the presence of urethral stricture, periurethral abscess, obstruction of Littre's glands, or chronic prostatitis. None of these 17 cases responded to treatment with penicillin alone and it was only after additional prolonged local therapy that they became culturally negative for *N. gonococcus*. Fourteen of these cases, although negative for *N. gonococcus*, continued to have a persistent chronic urethritis which was resistant to all types of therapy.

Summary and Conclusions

1. Of 500 consecutive sulfa-resistant cases of gonorrhea treated intramuscularly with 50,000 Oxford units of penicillin, 438 or 87.6 per cent became asymptomatic, culturally negative and were presumably cured.

2. Of the 62 cases of therapeutic failures after the initial course of penicillin, 45 were apparently cured after an additional course of 100,000 Oxford units, making a total of 96.6 per cent satisfactory results.

3. Seventeen cases of long standing chronic urethritis, originally on a gonorrheal basis but complicated by mixed infection, failed to respond satisfactorily to penicillin alone.

4. Penicillin did not have any specific effect on such complications of gonorrhea as acute epididymitis and arthritis in the few cases observed.

5. Except for the development of mild urticaria in five cases, there were no complications following injection of penicillin.

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THE CLINICAL INTERPRETATION OF INSULIN INDUCED KETONURIA *

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TRANSIENT ketonuria in association with aglycosuria observed in insulin treated diabetics presents an apparent paradox. Such an observation was not uncommon at the time protamine zinc insulin was becoming popular. As pointed out by Mirsky [1] the older theories concerning ketogenesis are still invoked whenever a clinical problem involving ketonuria is found. The standard texts on diabetes mellitus dwell lightly upon the newer concepts concerning ketogenesis. The significance of insulin induced ketonuria, therefore, is frequently misunderstood and the condition is treated by additional insulin.

In 1935 Somogyi [2] observed the "causal connection between hypoglycemia and ketosis." Since this time he has expanded his studies of this phenomenon.[3, 4] His work forms important supporting evidence for current concepts of ketogenesis. The clinical importance of these concepts will be demonstrated in this paper by a variety of cases in which we have observed acetonuria in association with hypoglycemia induced by insulin. In none of the cases were blood ketones determined so that the only evidence of increased blood ketone level was the finding of acetone in the urine. These cases illustrate the failure on the part of clinicians in general to appreciate the causes and clinical implications of this phenomenon. In reporting these cases the necessity for clinical alertness in recognizing this apparent paradox is emphasized.

CASE REPORTS

Case 1. A 40 year old male, whose past health had always been excellent, entered the hospital at 6:30 p.m. The family history was negative. For several days prior to admission he had noted increasing weakness, polyuria and polydipsia. He also complained of blurred vision and increasing drowsiness. Physical examination revealed an ambulatory, drowsy male. His sensorium was dulled but did not interfere with his coöperation. The pulse was 62, blood pressure 114 mm. Hg systolic and 74 mm. diastolic, respirations 28 per minute, and the oral temperature was 97.6° F. There was a marked acetone odor to the breath. The physical findings, in general, were normal. A number of sebaceous cysts were present.

On admission his blood sugar was 500 mg. per cent and a urinalysis revealed 4 plus sugar, 4 plus acetone and 4 plus diacetic acid. Facilities for determining CO_2 combining power were not available at that time. The diagnosis of diabetes mellitus was made and insulin therapy instituted. Seventy-five units of regular insulin were given in divided doses during the first four hours (table 1). Five hours after institution of treatment diacetic acid was no longer present, acetone was 3 plus, and sugar was 3 plus. Twenty units of regular insulin were given a half hour later and one hour after this an additional 10 units were injected. This was given although the

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response to treatment, which might have been suspected five hours after treatment began, was now definite in that the urine sugar and acetone had both decreased to 1 plus. Eight hours after treatment began 10 more units of regular insulin were given although only traces of sugar and acetone were present in the urine. The urine specimen, obtained before breakfast, revealed no sugar but a trace of acetone. A blood sugar taken before breakfast and before 20 units of regular insulin were given was 47 mg. per cent. The urine sugar remained negative one hour after breakfast,

TABLE I

Case F. J. B. Age 40 W— Ht. 70 Wt. 150		Urine			Diet: C 200; P 90; F 80		
Date	Time	Sugar*	Acetone	Diacetic Acid	Blood Sugar** Mg. %	Insulin	Misc.
4/18/44	6:30 p.m.	4+	4+	4+	(Admission) 500	RI U-40	
	7:20 p.m.	4+	4+	3+			
	8:20 p.m.	4+	4+	3+			
	9:00 p.m.					RI U-15	1 glass milk and 1 slice dry toast
	9:20 p.m.	4+	4+	3+			
	10:20 p.m.	4+	4+	1+		RI U-20	
	11:20 p.m.	3+	3+	Neg.			
	Midnight					RI U-20	
4/19/44	1:.0 a.m.	1+	1+	Neg.		RI U-10	
	4:00 a.m.	tr	tr	Neg.		RI U-10	Insulin given with breakfast
	7:00 a.m.	Neg.	tr	Neg.	47!	RI U-20	
	8:00 a.m.	Neg.	tr	Neg.			1 glass orange juice and 1 slice dry toast
	10:00 a.m.	tr	3+!	Neg.			
	11:00 a.m.	2+	1+	Neg.			
	Noon					RI U-20	Insulin given with lunch
	1:00 p.m.	2+	0	Neg.			

* Benedict Qualitative Technic.
** Venous Blood—Folin Wu Technic.

but showed a trace two hours after this. *However, the acetone showed an inordinate rise to 3 plus over the same time interval.* Additional carbohydrates in the form of orange juice and toast were given and, in response to this, one hour later the urine sugar increased to 2 plus but the acetone diminished to 1 plus. Following the noon meal, the acetone disappeared or was present only in traces despite a persistent glycosuria which ranged between 2 and 4 plus throughout the rest of the day.

The patient came under my observation on the third day of his illness and was regulated ultimately on a diet of 250 grams of carbohydrate, 100 grams of protein, and 100 grams of fat. Protamine zinc insulin U–15 was administered 45 minutes

before breakfast daily. On this regimen, the patient was usually aglycosuric and always ketone free. Nocturnal hypoglycemia did not occur as the blood sugar at 3 a.m. was 98 mg. per cent and the fasting blood sugar at 6:15 a.m. was 82 mg. per cent. The patient was discharged following an uneventful convalescence from surgical excisions of all sebaceous cysts.

Table 1 illustrates the pertinent features of this case during the ketotic stages of the first 24 hours. The initial ketonuria was caused by excessive glycogenolysis which was extreme because the patient was approaching diabetic coma. This initial ketonuria, therefore, is diabetic in origin. The response to the first 75 units of insulin was quite satisfactory but at this point a proper evaluation of the urinary findings would have led to more conservative use of insulin and the judicious addition of carbohydrate feedings at intervals. The excessive use of insulin which followed produced a hypoglycemic state which was proved by the 47 mg. per cent blood sugar level obtained before breakfast (7 a.m.). This was followed by a continued absence of sugar in the urine and a sudden increase in acetonuria. Thus, we note that there has been a secondary *increase* in acetone as the glycosuria *diminished* and this was followed by the disappearance of the acetone, although the glycosuria *increased* and remained elevated. This secondary increase in acetone is *not* a reflection of disturbed carbohydrate metabolism secondary to a diabetic crisis, but as the case illustrates, is the response to an *insulin induced hypoglycemic state*. A realization of this mechanism would have obviated the hypoglycemia and the resultant rise in ketonuria. The case demonstrated that the ketogenic action of insulin when used in excessive amounts interferes with the prompt and proper regulation of the diabetic patient and produces a misleading ketonuria.

Case 2. A 39 year old married female was seen for the purpose of changing her diabetic regimen from regular insulin to protamine zinc insulin. The patient was a known diabetic of eight years' standing. The disorder was discovered while the patient was recuperating from an appendectomy. Her family history was negative and the patient's past health had been excellent. The diabetes had always been asymptomatic. For two years she had been taking 10 units of regular insulin 20 minutes before each of three equicaloric meals. The diet was approximately 150 grams of carbohydrate, 70 grams of protein, and 100 grams of fat. For one month prior to observation her diet consisted of 210 grams of carbohydrate, 80 grams of protein, and 60 grams of fat supplemented by concentrated vitamins A and D. Several sets of 24-hour urines preserved with toluene were collected over two day periods and showed that the daily glycosuria ranged between 0 and 14 grams. The admission physical examination, routine blood counts and urinalyses were normal. During hospitalization the patient continued the same diet. Protamine insulin U–35 was given 45 minutes before breakfast. Urine specimens were collected from meal to meal and were examined quantitatively by the Somogyi technic.[5] The fourth night following daily injections of the 35 units of protamine zinc insulin a hypoglycemic state occurred (blood sugar at 3 a.m. 49 mg. per cent) and this was followed by the appearance of acetone in the urine (table 2, heavy bordered section). The insulin was reduced to 20 units and additional carbohydrates were given at bedtime. Nocturnal hypoglycemia was not present subsequently and the urines were always free of acetone. Fasting blood sugar on the two mornings prior to discharge on the eleventh day was 113 and 126 mg. per cent respectively. The glycosuria for each 24 hour period ranged between 21 and 15 grams with total available carbohydrate in the diet approximating 260 grams. The patient was instructed to continue on this regimen. No follow-up observations have been made but she was reported as remaining well.

In contrast to Case 1, this case shows that an appreciation of the ketogenic potentialities of insulin leads to a prompt reduction in the insulin. In this case, such a reduction was followed by permanent disappearance of ketonuria without sacrificing

the diabetic regulation. In fact, diabetic regulation was *improved* following the use of *less* insulin as judged by fasting blood sugars within the range of normal and a perceptible decrease in the total amounts of glycosuria for each succeeding 24 hour period (table 2). This case is typical of many cases observed by Somogyi [2] and by us.

TABLE II

Case F. C. W— Age 39 Ht. 61 Wt. 122	Fractional Urine Examinations								Diet: C 210; P 80; F 60		
	Breakfast to Lunch		Lunch to Supper		Supper to Midnight		Midnight to Breakfast				
Date 1943 September	G*	A**	G	A	G	A	G	A	Total Glycosuria Gm.	Blood Sugar*** Mg. %	Insulin, Etc.
17 to 18	12	0	14	0	6	0	0	0	32		6:15 a.m. 9/17/43 PZI U-35
18 to 19	23	0	18	0	4	0	0	0	45		No change
19 to 20	27	0	21	0	4	0	0	0	52		No change
20 to 21	16	0	14	0	7	0	0	+	37	3:00 a.m. 9/21/43 49	No change
21 to 22	18	tr	13	0	3	0	0	+	34	3:00 a.m. 9/22/43 62	6:15 a.m. 9/21/43 PZI U-25
22 to 23	16	tr	12	0	5	0	0	tr	33		6:15 a.m. 9/22/43 PZI U-20
23 to 24	19	0	5	0	3	0	0	0	27	3:00 a.m. 9/24/43 81	1 Orange h.s No change in PZI
24 to 25	18	0	3	0	tr	0	0	0	21		No change
25 to 26	13	0	2	0	0	0	0	0	15	6:00 a.m. 9/26/43 113	No change
26 to 27	17	0	4	0	0	0	0	0	21	6:00 a.m. 9/27/43 126	No change

* Glucose Expressed as Grams—Somogyi Technic.[5]
** Acetone Test (Denco).
*** Capillary Blood Analysis—Folin Micromethod.

Case 3. A 24 year old male first came under my observation during June 1943. His glycosuria had first been noted during July 1942 while he was hospitalized elsewhere because of an acute respiratory infection. The records of this hospitalization and subsequent out-patient care were made available to us. The patient's past history was irrelevant and his family history was entirely negative. Glycosuria was found on admission and on repeated examination. The patient admitted on direct questioning that polyuria, polydipsia, and polyphagia had been present for some time. The respiratory infection subsided promptly and the diagnosis of diabetes mellitus was made. The patient was placed on an unmeasured restricted carbohydrate diet, divided into four meals, and was given 5 units of regular insulin before each meal. Upon

discharge, he was advised to curtail carbohydrates and to eat three meals a day. He was instructed to modify a basic dosage of 10 units of regular insulin before each meal according to the results of urinalyses before each meal. The patient soon began to omit his breakfast insulin because his early morning specimens were consistently sugar-free. He discovered that periodic nervousness an hour after lunch and supper was relieved by reducing his insulin to 5 units before these meals. During May 1943, the patient complained of listlessness and fatigue upon arising. These complaints were frequently associated with early morning headaches. On May 6, 1943, a fasting blood sugar was 45 mg. per cent and the urine was sugar free but showed a trace of acetone. The patient was advised to start taking 5 units of insulin before breakfast and to continue with the same dosage before lunch and supper. His complaints continued and on May 30, 1943, a fasting blood sugar was 65 mg. per cent. *Again the urine was sugar free but showed a trace of acetone.* The patient was advised to continue taking 5 units of insulin before each meal because of the acetonuria.

The patient came under my observation during June of 1943 while hospitalized because of acute gonorrheal urethritis. This had completely subsided before I was asked to see the patient because of his purported diabetes mellitus. Physical examination was normal. The patient was placed on a diet of 250 grams of carbohydrate; 80 grams of protein; and 60 grams of fat. No insulin was given. The 24 hour glycosuria amounted to less than 10 grams and usually less than 5 grams. His early morning complaints disappeared immediately. Fasting blood sugars were normal and a carbohydrate tolerance test revealed that this patient's diagnosis was renal glycosuria.

Dose: 100 grams glucose.

Time	Blood Sugar*	Urine Sugar
Fasting	114 mg. %	0
½ hour	167 mg. %	Trace
1 hour	145 mg. %	Trace
2 hours	130 mg. %	Trace
3 hours	92 mg. %	0

* (Capillary blood sugar determinations by the Folin micromethod.)

The benign nature of the condition was explained to him and he was discharged with instructions to take no insulin unless further studies indicated need for it.

The failure to appreciate the cause of the ketonuria in this case is illustrated by the fact that in the face of acetonuria per se more insulin was advised. The low blood sugars confirm the impression that the patient was undergoing recurrent hypoglycemias, which were evidenced clinically by the patient's complaints. These comments are independent of the erroneous identification of glycosuria as diabetes mellitus. We may presume that in this individual the ketogenic factors operating in cases of diabetes mellitus could not have been present since we have shown that the carbohydrate tolerance curve was normal. Thus, by eliminating diabetes mellitus as a factor, the causal relationship between hypoglycemia and ketonuria is clearly illustrated.

Case 4. A 20 year old male patient came under observation during September 1943 because of a number of previous attacks of "blacking out," preceded frequently by automatic behavior. One such attack occurred September 1, 1943 while the patient was marching in a group to a classroom. His companions later told him that he had been marching as if in a daze and then fell to the ground unconscious. There was no convulsion. The family history was negative. The past history revealed that the patient had had pneumonia during childhood, with no sequelae, but

had experienced no other serious illness. At the age of 12, he was hit by a baseball and was unconscious for 10 minutes but recovery was complete.

The physical examination revealed an asthenic individual with no physical abnormalities. Blood pressure was 110 mm. Hg systolic and 56 mm. diastolic; pulse, 80; weight, 128 lbs.; height, 68 inches. An investigation of the patient's personality revealed that he had always been a tense, hyperkinetic individual who worried much over minor matters. Dreams of nightmare proportions were rather frequent. He admitted undue anxiety and tension whenever he was in the foreground and always preferred to remain in the background.

During the course of routine examination, the fasting blood sugar was found to be 65 mg. per cent (capillary blood). Blood Kahn reaction was negative. Radiographic studies of the skull revealed no abnormalities. He was subjected to a 24 hour fast, during which time his only complaint was mild frontal headaches and at the end of which time his blood sugar was 72 mg. per cent. The patient was then given a general diet for several days before a modified carbohydrate tolerance curve was obtained:

Dose: 50 grams glucose.

Time	Blood Sugar*	Urine	
		Sugar	Acetone
Fasting	74 mg. %	0	0
½ hour	112 mg. %	0	0
1 hour	88 mg. %	0	0
2 hours	49 mg. %	0	0
3 hours	52 mg. %	0	0
4 hours	53 mg. %	0	0
5 hours	60 mg. %	0	0
6 hours	60 mg. %	0	Trace
7 hours	52 mg. %	0	1 plus

* (Capillary blood sugar determinations—Folin micromethod.)

After the blood sugar level had remained at hypoglycemic levels for five hours acetone began to appear in the urine. Immediately following the seventh hour, the patient became extremely nervous and lost consciousness for a few minutes. He responded promptly to glucose by vein. A diagnosis of spontaneous hypoglycemia was made in the absence of findings pointing to organic disease.

The prolonged hypoglycemia observed during the latter part of the carbohydrate tolerance test resulted in the appearance of acetone in the urine. The patient was prepared for the tolerance test by the administration of a high caloric, high vitamin diet for several days before it was performed. Thus, we attempted to eliminate starvation as a factor in the ketogenesis. It is unfortunate that starvation cannot be conclusively eliminated as a factor because the blood sugar and urine acetone determinations were not made during the 24 hour fasts. Nevertheless, it is felt that in this case there was an insulin induced hypoglycemia followed by the appearance of acetonuria, the source of the insulin being endogenous. The initial dose of glucose stimulated an excessive secretion of endogenous insulin and the resultant hypoglycemia in turn brought about the ketonuria. Thus, this case supports further the idea of the causal relationship between insulin induced hypoglycemia and ketonuria.

Discussion

Collip [6] in 1922 was the first to observe experimentally that rabbits made hypoglycemic by insulin developed ketonuria. Mirsky [1] has pointed out that the older concepts concerning ketogenesis and ketolysis remain as the pre-

vailing point of view of the majority of clinicians. That this is true is demonstrated by the early management of Case 1 and Case 3 in which the appearance of acetone apparently was thought to be the result of the diabetic process and for which additional insulin was administered; whereas the correct interpretation should have dictated the administration of either no insulin or more carbohydrate or both.

Briefly, it is to be pointed out that the ketonuria in all these cases is a readily available clinical reflection of an increased blood ketone level which, in turn, is a reflection of increased fat metabolism in the liver, secondary to hypoglycemia. We do not mean to infer that every hypoglycemic state is followed by ketonuria, but a rise in the blood ketone level can often be demonstrated.[2] When insulin has been given in amounts such as to produce a hypoglycemic state, there is an exaggerated physiologic response which rapidly depletes the liver of its glycogen store. During such phases of glycogen loss, the liver begins to metabolize increasing amounts of fat (and protein). The ketonemic level at any given time depends on four factors which can be readily appreciated on the basis of the following diagram taken from Somogyi[3]:

Ketonemic Level			
Is Increased by		Is Decreased by	
Deglycogenation of liver, entailing an increase in its fat catabolism. (Factor I)	Decrease in rate of ketone utilization in extrahepatic tissues. (Factor II)	Increased CHO utilization in liver, which depresses fat catabolism. (Factor III)	Increase in rate of ketone utilization in extrahepatic tissues. (Factor IV)

That insulin may be either anti-ketogenic or ketogenic is not generally appreciated. The liver of the diabetic patient has a deficient glycogen store because in the diabetic organism glycogenolysis is accelerated. Insulin, in amounts sufficient to halt the glycogenolysis, will be anti-ketogenic since it favors glycogen deposition. Since the liver preferentially metabolizes carbohydrate, the metabolism of fat will decrease as glycogen becomes available. Conversely, following the exhibition of too much insulin, there is an excessive outpouring of glycogen from the liver in an attempt on the part of the organism to correct the hypoglycemic state. As a result of this outpouring of glycogen from the liver, fat metabolism is stepped up, the ketonemic level increases, and in the final analysis insulin has become ketogenic.[2] *

Four clinical experiences have been reported in which the common denominator is insulin induced hypoglycemia followed by the appearance of ketonuria. In two of the cases it has been pointed out that the failure to recognize the ketogenic potentialities of insulin has resulted in aggravation of the ketonuria. In our experience the combination of aglycosuria and ketonuria has frequently led us to find and correct insulin induced hypo-

* Mirsky's [1] paper gives a brief exposition of current theories concerning ketogenesis and ketolysis.

glycemias which had been occult. It is obvious that the avoidance of the hypoglycemic state in the diabetic patient is of extreme importance since repeated hypoglycemias will further deplete glycogen stores which are usually subnormal in the newly discovered diabetic organism.

Summary

Four cases have been presented in which aglycosuria and ketonuria were found following insulin-induced hypoglycemic states. Two of the cases reported were diabetes mellitus, one was a case of renal glycosuria and one was spontaneous (neurogenic) hypoglycemia. This demonstrates that the ketonuria described is not peculiar to diabetes mellitus but is the result of physiologic responses to the hypoglycemic state. The interpretation of this phenomenon has been discussed and its importance with particular reference to the management of diabetic patients has been pointed out.

Note: The author wishes to acknowledge gratitude to Dr. Michael Somogyi, under whose guidance was kindled an interest in and appreciation of the problems covered by this paper, and to Colonel J. S. Sweeney, M.C., A.U.S., Chief of the Medical Service, Bushnell General Hospital, for his constant encouragement and for his splendid clinical and editorial assistance.

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PICROTOXIN IN BARBITURATE POISONING*

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Picrotoxin as an antidote for human barbiturate poisoning was used first by Arnett [1] in 1933. Maloney, Fitch and Tatum [2] previously had demonstrated its effectiveness by animal experiments. In 1936 Koppanyi and his co-workers [3] definitely established its clinical value and proved its safety when administered properly. During the ensuing years the practical use of picrotoxin has been determined, particularly for those patients having a degree of narcosis approaching lethal levels.

The recent extensive review of the pharmacologic and physiologic aspects of the barbiturate problem by Tatum [4] and Richards' [5] clinical evaluation of picrotoxin in barbiturate poisoning agree in establishing it as the analeptic of choice in instances of dangerously deep depression. There is abundant evidence that other analeptics such as metrazol are effective in the barbiturate poisoned patient, but most of those with experience are in accord with the above authors that from the point of view of safety and sustained effectiveness picrotoxin is preferable.[5, 6, 7, 8] However, there still exists in many clinics an overcautious and at times almost unreasonable reluctance to employ this drug. Some physicians maintain that most patients suffering from barbiturate poisoning will recover eventually with supportive treatment supplemented by the less potent stimulants. This is undoubtedly true in many instances, but unfortunately is not always the case as may be seen by a review of a number of reports.

In New York City alone barbiturate suicides approximately doubled in the five year period from 1937 to 1941.[9] A five year study in Connecticut [10] revealed a mortality of 298 or 5.9 per cent in 1780 cases of attempted suicide with barbiturates. This includes all cases reported, many of which were not alarmingly narcotized. Other sources [5, 10, 11] report 6.5, 7.3, and 6.0 per cent fatalities. A mortality rate of over 6 per cent warrants the utilization of every merited therapeutic measure available.

The complications accompanying prolonged depression from barbituric acid derivatives cannot be ignored. Although some untreated patients recover from excessively large doses as illustrated below, the prolonged period of morbidity with its undesirable complications is to be avoided if possible. Prolonged hypoxia, intercurrent pulmonary infection, pulmonary edema, cerebral edema, nutritional deficiencies, depressed kidney function, decubitus ulcers and transient or more permanent neurological sequelae are the more frequent accompaniments of prolonged barbiturate narcosis.[5, 11, 12, 13]

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In discussing the advisability of picrotoxin therapy in given cases of poisoning, the impression frequently is gained that either a lack of familiarity with the drug, or a fear of its potency, or both are responsible for the reluctance to use it. To those familiar with its action and the method of administration there is no substantial reason to withhold it from patients for whom its use is indicated. It should be employed early and in adequate amounts supplemented by other supportive measures. The following typical case histories are presented in support of this contention.

Case Reports

Case 1. A 30 year old white female reported to have taken about 2.0 gm. of seconal came from another hospital where she had been admitted 24 hours earlier. No active treatment had been instituted although the patient was comatose upon admission. When transferred she was still in deep coma and gave no response to painful stimuli. The temperature was 100.6° F., pulse rate 78, and the blood pressure 100 mm. Hg systolic and 72 mm. diastolic. She was breathing deeply and regularly at a rate of 12 times per minute. The skin was of good color, warm and moist. Pupillary responses were variable. Both lung fields were filled with scattered rhonchi. Barbituric acid was found in the gastric contents and the urine. The blood concentration was 0.095 gm. per 100 c.c. Benzedrine, 0.02 gm., was administered on admission followed by caffeine sodium benzoate, 0.5 gm. every hour. Sulfadiazine routine was begun nine hours after admission. The only evidence of improvement was an occasional movement of the extremities during a two hour period beginning 10 hours after admission. The temperature gradually rose to 108° F., the pulse rate to 160, and the respiratory rate to 40 per minute. The patient died 15 hours after admission with a terminal picture of pulmonary edema. An autopsy revealed bilateral bronchopneumonia, pulmonary edema of the upper lobes, and slight pial congestion.

This is an example of the too frequent outcome of inadequately treated acute barbiturate poisoning. Although the patient had been comatose for at least 24 hours, her relatively good condition on admission points to the probability that with proper management the case might have terminated differently. Certainly experience suggests that the therapy was inadequate.

Case 2. A 29 year old white female was admitted to the hospital October 14 approximately 10 hours after taking 5.0 gm. of pentobarbital sodium as was learned from a subsequent history. She was deeply comatose, areflexic and unresponsive to all stimuli. The skin was slightly cyanotic, the pupils variable in size. The temperature was 102.6° F., the pulse rate 112, the blood pressure 96 mm. Hg systolic and 54 mm. diastolic, and the respiratory rate 28 per minute with shallow and slightly irregular breathing. Urine and gastric contents when analyzed were positive for barbituric acid. Initial therapy included gastric lavage, intravenous thiamine chloride 0.02 gm. every six hours, and metrazol, 2 c.c. hourly, ordered to be given until twitchings or convulsions occurred. Nine hours later breath sounds were absent over the left upper lobe, expansion of the right chest was greater than the left with shallow breathing at a rate of 34 per minute. Breath sounds returned in the left axillary area three hours later, at which time sulfapyridine therapy was begun. Metrazol was continued. Thirty hours after admission the temperature was 105° F., pulse rate 130, respirations 26 per minute. Metrazol, 11 c.c., was then given intravenously over a period of 42 minutes, resulting in leg movements, followed two hours later by occasional motion of all extremities and a return of the swallowing reflex. Pain stimuli still elicited no response. Two more intravenous doses of metrazol, 5 c.c. each, were then given an hour apart after which the analeptic was discontinued. Deep reflexes

returned 40 hours after admission with some spontaneous movements. Response to stimulation was absent until the fourth day, at which time left lower lobar pneumonia developed and the cough reflex appeared. The patient's condition remained essentially unchanged for three succeeding days, when the temperature began to fall and the lungs became less congested. At this time more vigorous vitamin therapy was instituted. Bullae which had appeared on the heels became infected and ulcerated. On October 21 the patient became more active. Two days later, nine days after admission, verbal contact was established and she awakened sluggishly. At this time a left foot drop was noticed. Following a slow convalescence the patient was discharged on November 23. Six days later she returned, was rehospitalized for two weeks, and then sent to a rest home for two months. At the end of this time the foot drop persisted, causing the patient considerable concern for fear that it would interfere with rehabilitation. Total hospitalization was 68 days, plus an additional and incomplete convalescence of two months.

The prolonged recovery time, the slow convalescence and the unfortunate sequelae suggest that one error in management was the postponement of adequate analeptic therapy. Thirty hours elapsed before the return of reflexes and motor activity, during which time pulmonary disease became established and the groundwork laid for other complications. Stimulants sufficient to establish and maintain reflexes and active movements are indicated as early therapy in every case.

Case 3. A 43 year old white female was admitted on April 4, 24 hours after ingestion of 4.25 gm. of pentobarbital sodium. Urinalysis revealed barbituric acid, 0.026 gm. per 100 c.c. During the first 18 hours of treatment she was given intravenous fluids, coramine, 1.5 c.c., and caffeine sodium benzoate, 1.0 gm. The treatment was then undertaken by another service. The patient was deeply comatose, slightly cyanotic and areflexic. The face was edematous. Temperature was 102.8° F., the pulse rate 120 and of a thready character. The breathing was a shallow type at a rate of 15 per minute and there were moist râles at both lung bases. Oropharyngeal oxygen by nasal catheter was ordered and intravenous picrotoxin was administered at the rate of 0.003 gm. per minute until 0.024 gm. was given. The patient then began to yawn, respirations increased in rate and depth, and the corneal and plantar reflexes returned. During the next 12 hours picrotoxin was given intramuscularly in 0.003 gm. doses every half hour, except once when depression deepened and 0.012 gm. was given intravenously. This was followed by active movements and occasional moans. Analeptic therapy was discontinued for 13 hours when deep narcosis again appeared. Picrotoxin, intramuscularly, was resumed in 0.003 gm. doses every half hour for the next nine hours, with one episode of regression when it was administered intravenously. A total of 0.238 gm. was used over this 36 hour period. Adequate intravenous fluids and vitamin therapy were maintained throughout. The patient became increasingly active, finally requiring restraints. Bullae of the ankles and legs demanded special care. Approximately 92 hours after taking the drug, the patient showed signs of awakening, and 12 hours later recognized her family. When fully conscious the patient complained of blurred vision, tingling of the hands and feet, and a sluggish memory. These symptoms decreased during convalescence, but were present in a minimal degree upon discharge on April 26.

Though delayed, the effectiveness of picrotoxin therapy is demonstrated by this report. Such treatment should be instituted at the earliest possible moment. Had it been done in this instance, experience with other cases warrants the conjecture that the result would have been more satisfactory. This is borne out also by the following history.

Case 4. A 27 year old white female was admitted at 5:30 a.m. in deep coma. Information was volunteered that she probably had taken pentobarbital sodium. This was confirmed subsequently, the amount being 9.0 gm. seven and one-half hours before

admission. Respirations ceased as the patient was brought into the emergency room. The skin was cyanotic and clammy, the pulse barely perceptible at 88 per minute, the rectal temperature was 98.6° F. Reflexes were absent, the eyeballs motionless, and the pupils moderately constricted. Two ampules of coramine intravenously and three intramuscularly produced a temporary slow, shallow breathing of three minutes' duration. Artificial respiration was instituted. A nasoendotracheal tube was inserted and the patient placed in a respirator. The cyanosis disappeared and the pulse improved in quality. Oxygen by catheter and intravenous glucose-saline were started followed by gastric lavage. Momentarily stopping the respirator caused reappearance of cyanosis with no evidence of spontaneous respiration. The areflexia persisted. The temperature gradually rose to 103.4° F. and the pulse to 120 during the next eight hours. After 12 hours without improvement, intravenous picrotoxin was started at the rate of 0.003 gm. per minute. Twenty-three minutes later after 0.06 gm. was given, slight twitchings of the eyelids and facial muscles began rapidly spreading to the shoulders and upper extremities. Picrotoxin was discontinued and the convulsive movements ceased. The corneal reflex returned but apnea persisted. An additional 0.012 gm. of picrotoxin was given intravenously and 40 minutes after initiation of analeptic therapy, the patient gave a deep sigh and resumed breathing. The rate was 28 per minute, the excursions normal. Picrotoxin was continued intramuscularly, 0.003 gm. every 15 to 30 minutes as indicated for the next five hours except twice when extremely shallow respirations responded promptly to intravenous therapy. At 12:30 a.m. all reflexes were present and the patient opened her eyes occasionally. Picrotoxin was discontinued, a total of 0.192 gm. having been given. At 3:30 a.m. the endotracheal airway was removed and one hour later, 24 hours after admission, the patient was awake. At 10:30 a.m. she sat up for a chest roentgen-ray and requested breakfast. The temperature was 100.8° F., pulse 100, respirations 24. Convalescence was uneventful and rapid. When interviewed three weeks later there was no evidence of inadequate recovery.

This patient on admission presented a picture similar to the other cases cited plus an added apnea which as far as can be determined is the only recorded case of complete respiratory arrest in acute barbiturate poisoning.[14] Supportive treatment for the first 12 hours was more nearly adequate and much more complete than was given to the other patients cited in this report. The duration of narcosis might have been less had analeptic measures been instituted immediately. However, the result was satisfactory.

Reviewing these four selected cases one notes that upon hospitalization their respective conditions were essentially similar. The effectiveness of the treatment employed for the patient in Case 4 suggests that the others were inadequately managed. It raised the question also whether more favorable results would have been possible had different therapy been employed. Furthermore, the fact that the amount of drug taken by the patient who died was four and one-half times less than in the case which recovered rapidly and completely, even though in the latter narcotization was of a degree sufficient to produce complete respiratory depression adds to the contention that analeptic therapy is imperative. The importance of the time factor is demonstrated also. Postponing treatment as was done in Case 3, and the failure to employ adequate quantities of an analeptic possessing maximum sustaining qualities for the patient in Case 2 surely contributed to the prolonged morbidity and unsatisfactory recoveries.

It is a foregone conclusion that the patient suffering from deep barbiturate depression should be afforded every advantage favoring rapid and complete recovery. The following régime summarizes the accepted procedures essential to proper handling of such cases. The condition of the patient when first seen and the response to therapy is, of course, to be used as an index in each individual instance.

1. *An adequate airway* must be established immediately and maintained throughout. Oropharyngeal toilet to remove all secretions is best accomplished by suction, to be repeated whenever necessary. A nasoendotracheal airway is always indicated for the comatose patient in whom cough and swallowing reflexes are absent. This affords both an unobstructed airway and a means for aspiration. The airway must be kept clear of secretions by catheter suction. Such suction is employed routinely every hour if no evidence of occlusion is present, more frequently if indicated. The suction catheter must be inserted to the distal end of the airway to insure against a gradual occlusion from deposition of secretions along its walls. The endotracheal tube is left in place until resumption of a vigorous cough reflex, which may occur in a relatively short time or which may not reappear for several days if analeptic therapy is delayed. The anesthetist must remove, clean and replace the tube regularly at intervals of not less than 12 hours. When the airway is removed, if signs of laryngeal edema appear, it must be replaced at once. This is a rare complication and occurs within 30 minutes, if at all. When reflexes are sufficiently active to prevent intubation, postural drainage is maintained by elevation of the foot of the bed. The necessity for frequent turning of the patient needs no explanation.

2. *Artificial respiration* may be necessary in bradypnea or when very shallow respiratory excursions are present. This is not usually required for any prolonged period if analeptic therapy is not delayed.

3. *Oxygen* by a properly placed, correct type of oropharyngeal catheter at a flow of six liters per minute affords an adequate concentration at the alveoli.[15] This combats existing hypoxia and prevents its continuation. The catheter must be kept free of secretions at all times. If an endotracheal tube is in place a No. 12 French catheter is inserted into it to a depth of 5 cm. without interference with respiratory exchange. A properly fitted mask may be used if desired. The combination flow-meter positive-pressure mask is preferred, permitting an accurate control of oxygen percentage and making possible immediate application of positive pressure should pulmonary edema develop.

4. *Gastric lavage* is performed to remove any remaining drug and to empty the atonic stomach. The contents are analyzed for barbiturate. Catharsis is advocated in some clinics, leaving 300 c.c. of sodium sulfate in the stomach for this purpose. The possibility of regurgitation and aspiration of gastric contents is a real danger in an unintubated, comatose patient, hence it is preferable to have the stomach completely empty rather than risk this complication. Tube feeding is condemned for the same reason.

5. *Analeptic therapy* should be conservative if reflexes are active and motor activity present. Vigorous treatment is for the deeply depressed patient. In such cases picrotoxin may be given in 0.001 to 0.003 gm. doses intravenously, or in 0.003 to 0.006 gm. doses intramuscularly every 15 minutes until the desired response is attained. This fractional method is not so effective as the continuous intravenous procedure, which is equally safe if employed with proper caution. The drug is administered at the rate of 0.001 to 0.002 gm. per minute until the corneal, swallowing or other reflexes appear, or until slight twitchings of the facial muscles occur. If given beyond this point convulsions may result. These usually are of a mild nature and gradually subside as the stimulant is destroyed. Should they be severe, or should milder ones maintain, an intravenous barbiturate such as sodium pentothal is given slowly just to the point of control. Once signs of reflex and motor activity return picrotoxin is continued intramuscularly in maintenance doses of 0.003 to 0.006 gm. each 15 to 30 minutes as indicated. Should regression develop the same dose is given intravenously until the desired plane of activity is reëstablished. Each case must be treated individually and the drug continued until active reflexes and involuntary movements are maintained.

Since the action of picrotoxin may be delayed for as much as 10 minutes, caution is to be exercised in its administration. Furthermore, the impression has been gained that the initial response to picrotoxin following depression from the longer acting barbiturates is slower than is the case with the shorter acting ones, hence the analeptic should be given in smaller amounts if its accumulation with a resultant sudden and severe stimulation is to be avoided. Convulsions, if they occur, usually are followed by a degree of depression deeper than that existing before their onset.

The amount of picrotoxin necessary to establish the desired plane of activity is unpredictable. The wide variation in dosage seemingly bears little relation to the quantity of barbiturate taken. Although 0.02 gm. of picrotoxin is dangerously toxic to a normal adult,[16] doses ranging from 1.079 to 2.296 gm. have been employed for patients poisoned by barbituric acid derivatives.[17, 8]

6. *Intravenous fluid* therapy should not be delayed. Not only does this afford a route for the administration of analeptics, but insures proper hydration and nourishment and enhances renal function. Should prolonged venoclysis be necessary, adjustment to the needs of the individual patient is most important. Fluids must be administered judiciously if pulmonary edema is to be avoided. Two liters of 5 per cent glucose in normal saline with 1 liter of 5 per cent glucose in water given slowly meet the 24 hour requirements of the average patient.

Prolonged coma demands special attention to needs other than fluid and carbohydrate requirements and electrolyte balance. A positive nitrogen balance is maintained by intravenous amino acid therapy with an average dose of 70 gm. per day. This can be given separately in a 5 to 10 per cent solu-

tion or mixed with the glucose-saline infusion. To avoid urinary spill the rate of flow should be adjusted to not more than 20 gm., preferably less, in two hours, the total amount being divided into three equal portions started at eight hour intervals. The amino acids are utilized by the body for protein synthesis, sparing the body tissues against breakdown for energy production.[18, 19]

Vitamin therapy is indispensable if normal metabolism is to be approximated and neurological complications prevented in the patient who remains comatose for more than 24 hours. Parenteral thiamine chloride 0.005 gm., riboflavin 0.005 gm., and nicotinic acid 0.05 gm. given three times daily afford an adequate quantity of the B complex. They may be given in combined form. Sufficient vitamin C is insured by 0.10 gm. of ascorbic or cevitamic acid daily. In addition to its usual functions, Richards [20] demonstrated that vitamin C shortens the narcosis induced by the shorter acting barbiturates such as nembutal.

Circulatory collapse, should it appear, requires prompt antishock therapy with adequate amounts of plasma and the other supportive measures usually employed.

7. *Chemotherapy* is instituted should signs of pneumonia or other intercurrent infection appear. Pneumonia may be hypostatic, lobar or from aspiration. Early stimulation therapy, properly controlled fluid intake, and the prevention of aspiration usually will prove prophylactic against pneumonia, pulmonary edema or pulmonary abscess development.

8. *Diuresis* may be enhanced by intravenous fluids and diuretics should depression of urinary output occur. Many patients are incontinent, although others may require catheterization every 10 hours to prevent bladder distention and to be certain that kidney function is adequate.

9. *Nursing care* must be of the best with constant attention to all details, if good results are to be obtained. Oral hygiene, padding of pressure points to avoid decubitus, protection of the frequently appearing bullae, reduction of marked hyperthermia and protection of the patient against injuries once motor activity is resumed warrant special emphasis. Once consciousness returns psychiatric problems may arise which will require expert handling by both the physician and nurse.

Summary

The therapy of barbiturate intoxication is an increasingly important problem confronting the medical profession. There is a hesitancy on the part of some to employ the more potent analeptics and to institute certain other supportive therapies available. Four cases essentially similar are presented to illustrate the effects of neglected, inadequate, delayed and more immediate treatment. A suggested therapeutic régime is outlined. Early and adequate analeptic therapy with picrotoxin may prevent death, obviate a prolonged illness and result in a complete or more nearly complete recovery. Each case must be judged by the condition of the patient when admitted to

the hospital and managed according to the response shown toward undelayed treatment. If this is prompt, the more expensive and time consuming measures should not be necessary.

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DEMONSTRATION OF VISCERAL PAIN BY DETERMINATION OF SKIN POTENTIALS*

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The need of a method that permits one to demonstrate and to localize pain objectively in disease of internal organs is particularly striking under conditions such as the present national emergency. Every day the physician is confronted by the question as to whether the complaint of pain in a certain area is caused by an organic disease or whether it is of a psychic nature.

The need for an objective "pain-detector" is at least partly met by the measurements of the so-called viscerogalvanic reaction (Spiegel and Wohl). These authors studied the electrical potentials of the skin in cases of visceral pain and often found increase of these potentials in the area corresponding to the diseased organ. They explained the reaction due to reflex excitation of the sweat glands in the respective dermatomes, an excitation that is sustained by continuous impulses from the pathologic viscus. These studies were confirmed by findings of Guttmann who demonstrated colorimetrically, in cases of gall-bladder disease, disturbances of the sweat secretion in the corresponding dermatomes by the chinizarin method.†

In the present study we tried to ascertain whether the viscerogalvanic reaction may be an aid in the differential diagnosis between pain in organic visceral disease and that in non-organic disorders.

Method. The method is that used by Spiegel and Wohl with further modifications. A known variable potential is opposed to the unknown skin potential (compensation method figure 1). The known potential is varied until both potentials are equal, so that a zero instrument (string galvanometer, Leeds and Northrup portable galvanometer) shows no deflection. The principle is similar to that used in electrocardiography when the skin potentials are neutralized. In fact, the neutralizer of an electrocardiograph can be used for this purpose, if one standardizes its various positions in millivolts. Zinc-zinc sulfate electrodes were used as nonpolarisable electrodes. An amalgamated zinc rod dips into a glass tube I containing a saturated zinc sulfate solution (figure 2). The lower end of tube I is closed by a cellophane membrane separating it from a normal KCl or physiologic saline solution that is contained in a second glass tube. The lower end of glass tube II is also closed by a cellophane membrane; it is

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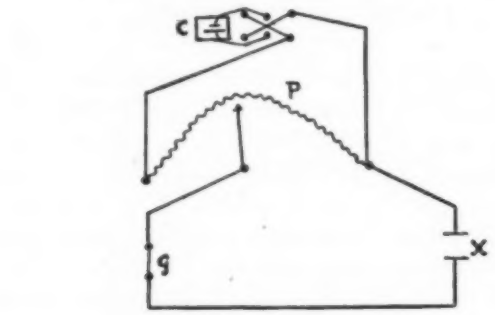
† Recently Portnoy found a positive viscerogalvanic reaction in 70 per cent of the cases of visceral pain studied.

to be applied to the skin. The testing electrode which is held by a handle is counterbalanced by a weight, so that it can be applied to the various areas to be tested with minimum pressure. This is important because pressure reduces or distorts the skin potentials. The indifferent electrode fits into a holder that can be strapped to the dorsal aspect of the forearm under con-



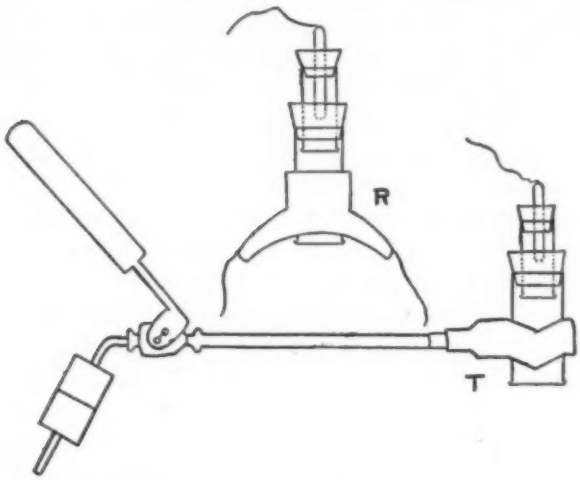


FIG. 1a (*above*). Principle of compensation method.
C—dry cell, G—galvanometer, P—potentiometer, X—unknown skin potential.
FIG. 1b (*below*). Unpolarisable electrodes.
T—testing electrode, R—reference electrode.

stant pressure so that the reference point has as low a potential as possible. Other measures which contribute toward successful results are: (1) the patients should be kept relaxed in a recumbent position in a warm room; (2) the testing electrode should be applied to each area for about the same length of time; (3) the testing electrode should be kept away, insofar as possible, from direct application to a hairy area; (4) excessively hairy areas should be shaved first and the testing done three or more days later.

Material. A series of 62 patients and 10 healthy, asymptomatic subjects was tested, making a total of 72 subjects.

In group I were 31 cases with pain accompanying proved organic disease (tables 1 and 2).*

The diagnosis was established after complete digestive tract studies were made, in addition to the history and physical examination, including gastrointestinal roentgen-ray series, cholecystograms, barium enema, blood Wassermann reaction, blood count and urinalysis. In certain cases, additional studies were carried out such as electrocardiography, gastroscopy, gastric analysis and biliary drainage. In this group are also included four cases

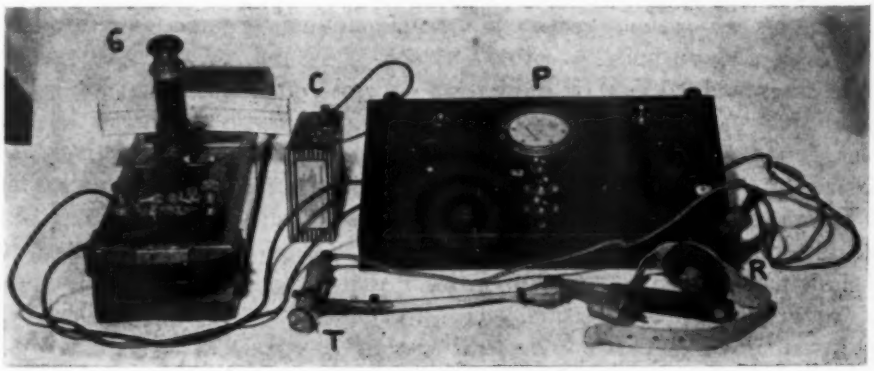


FIG. 2. Arrangement of apparatus.
C—dry cell, G—galvanometer, P—compensating circuit with potentiometer, R—reference electrode, T—testing electrode.

whose primary illness was a colitis (non-ulcerative, non-specific). Although these cases were non-ulcerative and non-specific and are generally recognized as being "functional" in nature, they were included in this group since, besides roentgen-ray findings such as loss of normal haustral markings, "string sign" or marked spasticity or irritability, definite inflammatory signs were present on proctosigmoidoscopy, such as edema of the mucosa, congestion, abnormal friability and bleeding of the mucosa. In cases 1 and 17, in which chronic gastritis was present, the diagnosis was arrived at after gastroscopic examination in addition to the roentgen-ray and gastric analysis studies.

Group II comprised 27 cases and consisted of patients suffering from such disturbances as neuroses, of whom there were 13 cases, and patients, who were symptom-free, but had had some organic disease at a previous date (table 3). In the group of patients with neuroses, vague aches and pains were complained of. These non-characteristic distress symptoms were judged to be of psychic origin from the historical and physical findings, as well as the roentgen-ray and laboratory findings.

Finally, four patients were studied in whom organic disease had recently existed (from three to six months prior to testing date), who were symptom-free for several months, but still showed abnormal skin potentials (table 4).

* In order to save space the tables have been omitted, but they will be included in the reprints.

Results. In 10 normal individuals the potential measurement on trunk and extremities except fingers varied between zero and five millivolts.* Our pathological observations are recorded in tables 1–4. It seems advisable to differentiate the areas tested into two groups. First, the areas where pain is felt (or the dermatomes corresponding to the diseased organ) may be called the P (pain) areas. Second, the remainder of the body surface may be called the R (remainder) areas. The difference D between the maximum potentials of the P (pain) area and R (remainder) area is indicated in each case in tables 1–3.

Among 31 patients with pain accompanying organic visceral disease (tables 1, 2), we find 23 with D values of 10 mv. or above 10; nine of these cases had 20 mv. or more. In contrast, among 27 patients without demonstrable organic disease (table 3), in no case was a D value of 10 mv. or over found. In two cases D values of 8 and 9 mv. respectively were observed,† while in the other patients in this same group D was 0 mv. Thus, if D values of 10 mv. or above are recorded, such observation may aid in the differential diagnosis between organic visceral pain and pain of non-organic nature such as "psychic" pain, in that it may support the assumption of an organic visceral lesion. However, in some cases, D values below 10 mv. may be observed in organic visceral pain as well as in non-organic pain.

The fact that in a number of cases of organic visceral pain a definite increase of skin potential in the respective dermatomes failed to appear is not surprising. It should be borne in mind that reflex effects upon vegetative organs such as the sweat glands depend not only on the intensity of the afferent impulses, but also upon the state of excitability of the vegetative effector organs. It seems that under certain conditions the pathologic afferent impulses are even able to inhibit the activity of the sweat glands, as demonstrated by a case of gall-bladder disease recorded by Guttmann. Consequently, diagnostic conclusions should not be drawn from negative results of the viscerogalvanic reaction; the lack of increase of skin potentials does not exclude an organic visceral lesion. Only positive results should be regarded as useful in that they indicate an organic visceral disease if the D value exceeds 10 mv.

Of special interest are the observations that are summarized in table 4. These are cases of organic visceral disease that were clinically "healed" or in a latent stage. The respective dermatomes showed increased potentials as compared with the rest of the body (D values in two cases were 10 and 13 mv. respectively and 7 mv. in two other cases). These findings indicate that after apparent healing from a clinical point of view, abnormal impulses

* Face, palm of hand, sole of the foot normally may show high potentials and, therefore, were usually not measured.

† The finding of potential differences in these cases is perhaps due to instability of the reference point. As pointed out by Snodgrass, Rock and Menkin in their study of ovulation potentials, emotional factors may cause such an instability, but this is insufficient to place the readings within the range of organic disease values.

may still originate in the respective organ or in scar tissue within or around the affected organ and may still maintain, at least for some time, a tonic excitation of segmental centers of the spinal cord, although these impulses may be below the threshold of the higher centers upon which conscious pain sensation depends.

Summary

1. The study of skin potentials is an objective method useful in the evaluation of visceral pain in 74 per cent of the 31 cases with pain accompanying proved organic visceral disease, there was an increase of the skin potentials in the respective dermatomes over the remainder of the body by 10 or more millivolts.

2. Twenty-seven cases with pain of psychogenic origin or healed organic disease revealed two single instances showing potential increases of 8 and 9 millivolts respectively, while the other 25 cases gave no increase of potentials.

3. Increase of skin potentials by 10 mv. or over in the dermatomes corresponding to an organ causing pain supports the assumption of organic disease. Lack of increased potentials does not exclude organic disease.

4. After apparent clinical healing of organic visceral disease, increased potentials may still persist indicating latent pathological changes.

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HYPERVITAMINEMIA A IN THE RECOVERY STAGE OF VARIOUS DISEASES*

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Various investigators have found that following a transitory stage of hypo- or avitaminemia-A at the height of the disease the blood vitamin A level rises in the convalescent stage to higher levels than normal and returns to the normal level some time after complete recovery. Such behavior has been described in the convalescent stage of acute hepatitis,[1, 2, 3, 4] in the recovery stage of pneumonia,[2, 3, 4, 5] and in febrile conditions.[4, 6, 7] Since this occurrence appeared of clinical interest, the present study was undertaken to determine the incidence, significance and specificity of this phenomenon and its relation to liver function and to the response of the plasma vitamin A level to the intake of 75,000 units of vitamin A (tolerance curve).

Material and Method

This study is based on observations on 35 patients who had at least temporarily a plasma vitamin A level above 50 micrograms and who were selected from a group of 189 patients of a charity hospital on whom serial plasma vitamin A determinations were made. The control cases of this group are composed of patients with hernia, fracture, compensated cardiac conditions and arthritis. They had an average plasma vitamin A level of 32 micrograms/100 c.c. Hence, a plasma vitamin A level of above 50 micrograms was assumed to be higher than normal, especially since many of the above mentioned patients were suffering from diseases characterized by a low or zero plasma vitamin A level during their height. Not included in this group are patients with elevated plasma vitamin A level following ingestion of large doses of vitamin A and patients with nephritis, the latter being discussed in another publication.[8]

Many of the selected patients had low or zero plasma vitamin A levels when their observation began. Some of them had plasma vitamin A levels within normal ranges at the start of the study. However, they were already in an improving stage of a disease in which low plasma vitamin A levels are characteristically present during its height. Others were in the convalescing stage of the disease, with plasma vitamin A levels much above

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the normal. Determinations of the plasma vitamin A level were done at one to three day intervals over a period of one week to three months depending upon the time when the blood level returned to within normal ranges or upon the time when the patient left our observation.

The determinations of plasma vitamin A and carotene were done by means of the Carr-Price reaction according to the method of Kimble.[9] The readings were made either by means of the Sheard-Sanford photolometer or the Coleman spectrophotometer or by copper sulfate standards according to a modification [10] of the method of Josephs.[11] The three methods checked satisfactorily. The values were given in micrograms per 100 c.c. plasma. The tolerance curves were performed by determining the plasma vitamin A level before, and 3, 6 and 24 hours after the administration of 75,000 I.U of vitamin A esters * in 2 c.c. corn oil. In some of the patients the following determinations were made to evaluate hepatic function: Total cholesterol, cholesterol esters, hippuric acid excretion, cephalin-cholesterol flocculation test and albumin/globulin ratio.

Results

The greatest number of the 35 patients with hypervitaminemia studied had various types of liver diseases (table 1). In them the greatest difference between previous levels and the highest plasma vitamin A level was encountered. Less marked was this difference in pneumonia, and postoperative

Table I

Tabulation of Patients in Whom Transient Hypervitaminemia A Was Observed

Diagnosis	No. Cases	Average No. of Determinations	Average Level in Hypervitaminemia Stage (Micrograms per 100 c.c. Plasma)	Maximal Difference Encountered in Plasma Vitamin A Levels
Arthritis	1	10	67	14
Fractures	2	10	57	23
Post-operative	3	8	83	72
Obstetrical	9	3	58	52
Pneumonia	2	10	69	69
Cirrhosis	7	11	82	117
Hepatitis	8	8	93	113
Incomplete Obstruction	3	8	71	67

or postpartum conditions. The difference in the vitamin A levels in one case with arthritis or two with fractures was less significant, especially since they were found among eight cases of arthritis and among 20 cases of fracture studied.

The stage of the disease in which hypervitaminemia-A occurs is demonstrated by the serial determinations of the plasma vitamin A level. In

* Distilled vitamin A concentrate (natural ester form distilled from fish liver and vegetable oil) containing 200,000 U.S.P. XI units per gram, generously supplied by Distillation Products, Inc., Rochester, N. Y.

patients with acute hepatitis, the hypervitaminemia stage occurs at the time when the icterus index returns to normal levels, i.e., in the beginning of the convalescent period; when the patient is cured, the plasma vitamin A level returns to normal (figure 1). Some cases of acute hepatitis came under our observation during the recovery period and the liver function tests were already normal. In these the plasma vitamin A level was rising at a time

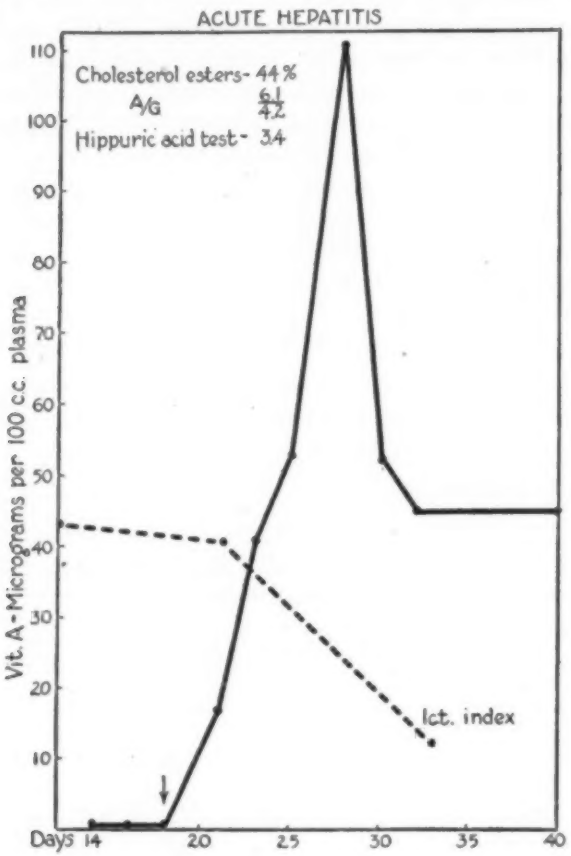

FIG. 1.

when the icterus index was returning to normal (figure 2). In cirrhosis a similar situation may be encountered with the difference that the period of hypervitaminemia A may be extended for long periods (figure 3). The hypervitaminemia A stage may even occur repeatedly (figure 4).

A similar situation was observed in patients with pneumonia in whom the plasma vitamin A level rose during recovery at about the eighth day of the disease (figure 5). Since these patients left the hospital relatively soon after the acute stage, we do not know when the plasma vitamin A level returned to normal. Similar tendencies in the plasma vitamin A level to rise above

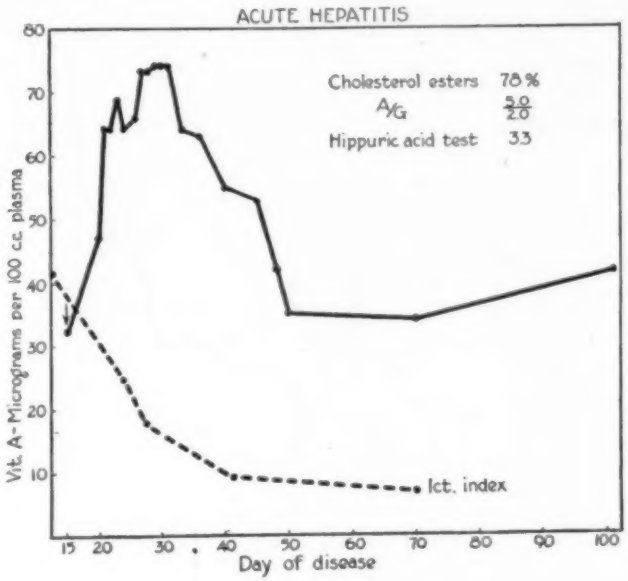
ACUTE HEPATITIS
Cholesterol esters 78%
A/G 5.0/2.0
Hippuric acid test 3.3
Vit. A - Micrograms per 100 c.c. plasma
Ict. index
Day of disease
10
20
30
40
50
60
70
80
15 20 30 40 50 60 70 80 90 100

FIG. 2.

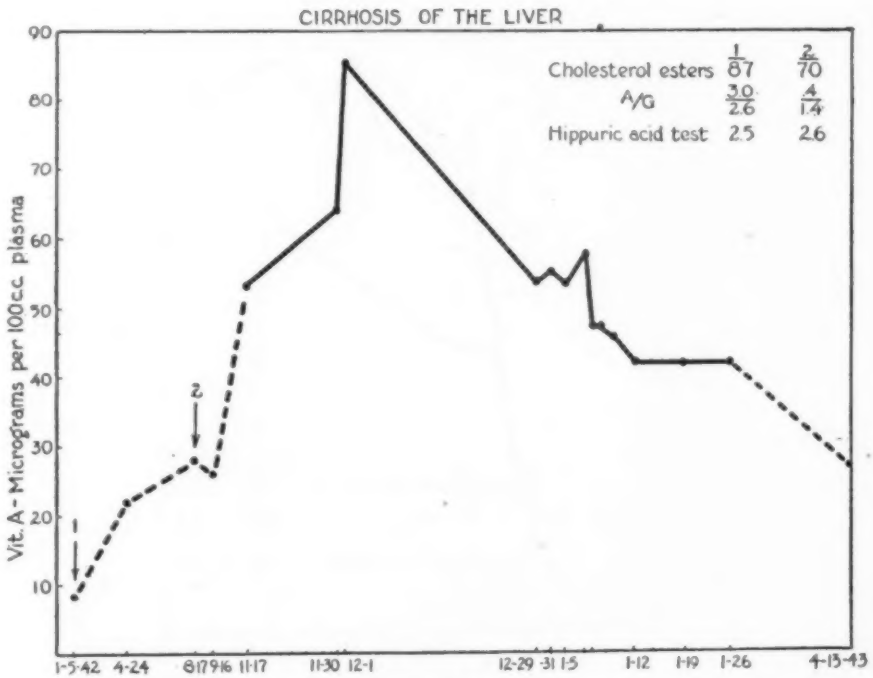
CIRRHOSIS OF THE LIVER
Cholesterol esters 1/87 2/70
A/G 3.0/2.6 4/1.4
Hippuric acid test 2.5 2.6
Vit. A - Micrograms per 100 c.c. plasma
1
2
10
20
30
40
50
60
70
80
90
1-5-42 4-24 8 17 9 16 11-17 11-30 12-1 12-29 -31 1-5 1-12 1-19 1-26 4-13-43

FIG. 3.

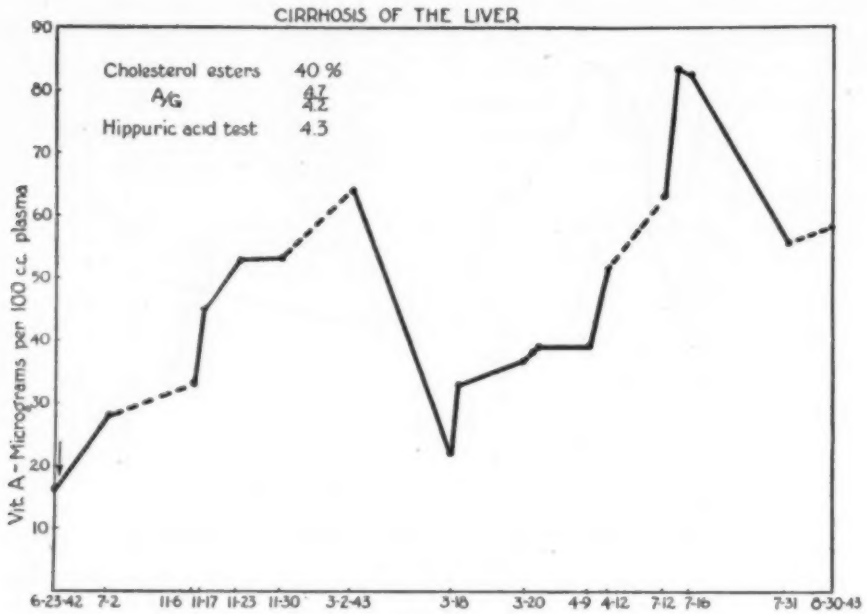
CIRRHOSIS OF THE LIVER
Cholesterol esters 40 %
A/G 4.7/4.2
Hippuric acid test 4.3
Vit. A - Micrograms per 100 c.c. plasma
90
80
70
60
50
40
30
20
10
6-23-42
7-2
11-6
11-17
11-23
11-30
3-2-43
3-16
3-20
4-9
4-12
7-12
7-16
7-31
8-30-43

FIG. 4.

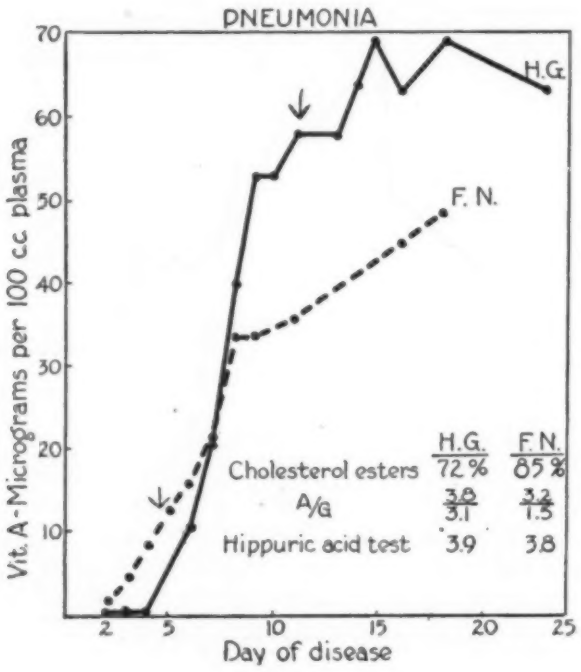
PNEUMONIA
H.G.
F. N.
Vit. A - Micrograms per 100 c.c. plasma
70
60
50
40
30
20
10
H.G. F.N.
Cholesterol esters 72 % 85 %
A/G 3.6/3.1 3.2/1.5
Hippuric acid test 3.9 3.8
2
5
10
15
20
25
Day of disease

FIG. 5.

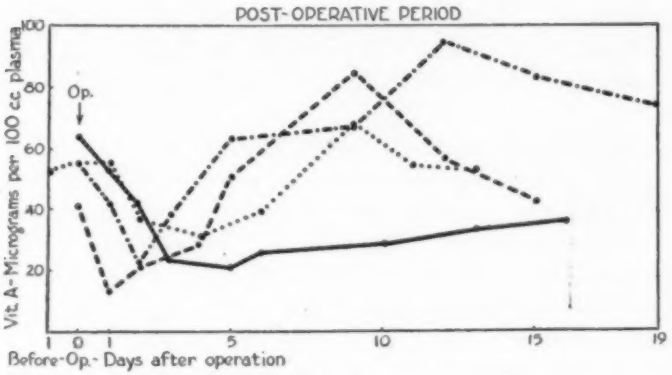
POST-OPERATIVE PERIOD
Vit. A-Micrograms per 100 c.c. plasma
100
80
60
40
20
Op.
1 0 1 5 10 15 19
Before-Op.- Days after operation

FIG. 6.

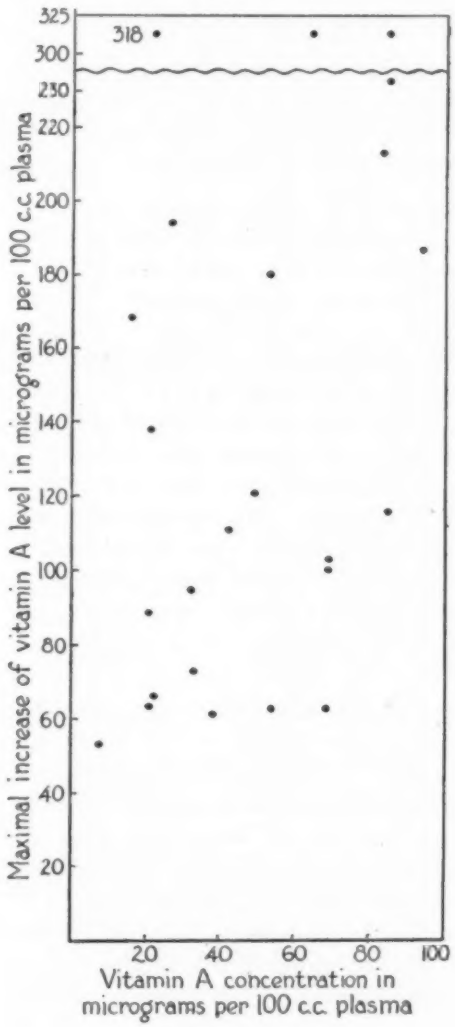
325
300
230
220
200
180
160
140
120
100
80
60
40
20
318
Maximal increase of vitamin A level in micrograms per 100 c.c. plasma
20 40 60 80 100
Vitamin A concentration in micrograms per 100 c.c. plasma

FIG. 7.

the normal following the initial drop were observed in patients following extensive abdominal operations. The hypovitaminemic stage was observed within 72 hours, and the hypervitaminemic stage was seen at about the tenth day (figure 6).

From the few representative cases in figures 1, 2, 3, 4 in which arrows point to the date when liver function tests were performed, it appears that the liver functions were normal when the plasma vitamin A levels were returning to the normal ranges. The results of the cholesterol esters partition and total plasma protein determination in these patients at different plasma vitamin A levels show that the percentage of cholesterol esters and the total plasma protein increase progressively with a rise in the plasma vitamin A level (table 2). In figure 7 the maximal increase in the tolerance curve is plotted against the plasma vitamin A level. From it a tendency toward higher tolerance curves in the hypervitaminemic stage seems to be apparent.

TABLE II

Comparison of the Plasma Vitamin A Level with the Percentage of Cholesterol Esters and the Total Plasma Protein Concentration

Vitamin A Level Micrograms Per Cent	Cholesterol Esters Percentage	Total Plasma Protein Grams Per Cent
0 to 20	55	6.5
21 to 50	73	6.8
50+	72	7.7

DISCUSSION

The presented data indicate that marked changes of the plasma vitamin A level may occur which are independent of the nutritional intake. There is no reason to believe that such abrupt changes in the plasma vitamin A level should occur from variations in nutrition which are of a comparatively moderate degree and short duration as seen, for instance, in acute hepatitis, pneumonia, or during operation. We must assume, therefore, that processes within the body govern the plasma vitamin A level.[4] The significance of endogenous in contrast to nutritional factors in the development of conditioned vitamin A deficiency has recently been stressed.[12]

The endogenous forces causing these changes seem to be multifold. Clausen et al.[13] were of the opinion that in the convalescent stage the intestinal absorption, which was impaired during the height of the disease, was already improved whereas the storage ability of the liver was still impaired, thus disturbing the normal balance between absorption and deposition in the liver. Liver function impairment is doubtless the cause of the reduction of the plasma vitamin A level but no indications from the liver function tests were obtained which would suggest that it is responsible for the hypervitaminemia A. The fact that the plasma vitamin A level rises abruptly during the beginning of improvement in cases of hepatitis or pneumonia, at a time when the diet of either is essentially high in protein and carbohydrate and low in fat, would point more to a sudden release of vitamin A

from the liver into the blood stream rather than to increased absorption. We [4, 14] suggested the possibility that the hypervitaminemia A is due to an increased release of vitamin A from the liver where it was retained in pathologic sites from which it cannot be utilized during the height of the disease.[15, 10, 16] For this fact speaks also the observation that in the acute stage of pneumonia or acute hepatitis the liver stores are not necessarily reduced.[3, 17, 18, 19, 20] A possibility of disturbed liver function with consequent displacement of the liver vitamin A in the acute stages and release during recovery stage can be assumed for other conditions than pneumonia and hepatitis. Furthermore, the observations of Josephs [5] that in infants below two years of age this hypervitaminemia is not as marked, which he explains on the lower available liver vitamin A depots in this age group, is one more evidence for liver release. Lund and Kimble presented evidence for a similar phenomenon in parturient women.[21]

However, the fact that the response of the vitamin A level to the intake of high doses of vitamin A is higher during the hypervitaminemic stage points to the existence of other factors, especially if we exclude liver damage with associated inability to store vitamin A as one of the causes of hypervitaminemia. An improved function of the intestinal tract is probably not the cause. An increased ability of the blood to carry vitamin A or a reduced destruction of vitamin A might be considered as has been done for conditions in renal disease.[8] Recent studies on the anti-oxidative activity of tocopherol (vitamin E),[22, 23, 24] which acts as a co-vitamin, has focused the interest upon processes which protect or destroy vitamin A in the body.

The hypervitaminemia A is not specific for any one disease and it could thus be an unspecific reaction of the body to a previous hypovitaminotic phase without any relation to the nature of the disease, a possibility which Josephs [5] pointed out and associated with the difference in adjustment to vitamin A intake in the hypovitaminotic stage. It was also observed [25] that the blood vitamin A level of normal adults rises to supernormal levels after a period of vitamin A depletion with consequent low vitamin A levels.

Whatever the cause of this phenomenon, it undoubtedly indicates a good prognosis inasmuch as it suggests that the patient is on the road to recovery.

Summary and Conclusion

The occurrence of a phase with hypervitaminemia A in various diseases is discussed. This phenomenon is due to endogenous factors and not to nutritional change.

One of these factors seems to be an increased release of vitamin A from pathologic sites in the liver to which it was shifted during the acute stage of the disease. Other factors appear to be increased ability of the blood to hold vitamin A or reduced destruction of vitamin A. Finally, a nonspecific "pendulum swing" like response to a previous low of the plasma vitamin A level has to be considered as a valuable prognostic sign.

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THE PROTHROMBIN RESPONSE TO LARGE DOSES OF SYNTHETIC VITAMIN K IN LIVER DISEASE*

By SHEPARD SHAPIRO, M.D., *New York, N. Y.*, and RICHARD K. RICHARDS, M.D., F.A.C.P., *North Chicago, Illinois*

THE liver is a most versatile organ. Its activities include various types of cellular physiology, principally synthesis, storage, conjugation, catabolism and excretion. Although subject to humoral influence, the functions, nevertheless, appear to be devoid of interdependence. However, despite the "dissociation," [1] certain of the mechanisms exhibit with significant constancy a higher degree of susceptibility to pathologic change than the others. Recently, Drill and Ivy [2] found abnormal retention of bromsulphalein to be the earliest detectable alteration in function following the production of liver damage in dogs by the administration of carbon tetrachloride.

At the time the paper by Drill and Ivy [2] appeared we were engaged in a similar study in both dogs and man. It is desired in this communication to present the results of our experiments.

The purpose of the investigation was to determine the behavior of the prothrombin level in liver disease artificially induced in dogs and occurring clinically in man; and the effect of large doses of synthetic vitamin K in such conditions. The study included serial estimations of the prothrombin time before and after the repeated administration of synthetic vitamin K. In some of the clinical cases and in the dogs the comparative sensitivity of other liver function tests was determined also, especially bromsulphalein retention.

OBSERVATIONS IN DOGS

Liver damage was produced in dogs by oral administration of 1 c.c. per kg. of a 50 per cent solution of CCl_4 in oil at intervals of three to four days. Eight dogs were used weighing between 4.5 and 10 kg. The animals were kept on a diet of Purina Checker Dog Food. CCl_4 was given to all of the dogs on the third, seventh, eleventh and fourteenth days after the initial dose. Injections of synthetic vitamin K (Hykinone)† were given to dogs 3, 6, 7, 8 (see table). The animals yielded evidence of liver damage by retention of the dye. The remaining dogs which had suffered degree of injury were used as controls and were not given Hykinone. The dose of Hykinone used was 15 mg. per kg. on the first two days and 10 mg. per kg. daily for the remainder of the experiment.

* Received for publication September 16, 1944.
This is No. VIII of the series "Studies in Prothrombin."
† Hykinone = Menadione — sodium bisulfite prepared by the Abbott Laboratories.

Determinations of bromsulphalein retention were made before, during, and after the experiment, as shown in the table, by injection of 5 mg. per kg. of the dye intravenously and determination of retention in the serum 30 minutes after the injection. The retention of less than 10 per cent was con-

TABLE I

Dog No. and Weight	Days											Remarks
	1	2	4	6	8	11	12	14	16	19	22	
1 6.9 kg.	CCl_4 given to all dogs	12 19 10%	CCl_4 given to all dogs	11 19 10%	CCl_4 given to all dogs	9 20 40%	CCl_4 given to all dogs	9.5 18.5 10%	CCl_4 given to all dogs	7 22* 10%	9 20 10%	
2 4.54 kg.		10.5 17.5 10%		11 21.5 15–20%		8.5 21 45%						Died on 13th day
3 10 kg.		11.5 19 10%		10 23 10–15%		9 16.5 10%		11 15 10%		7 15 10%	9 18 10%	Hykinone on 12th until 18th day
4 5 kg.		12.5 21 10%		12 27 10%		8.5 20.5 20%		11 26 30%		9 23 10%	9.5 22 —	
5 6.37 kg.		10.5 17.5 10%		9.5 20 10%		7 17 10%		8.6 20 60%		6.5 17* 10%	9 18 10%	
6 5.45 kg.		11 18 10%		18 70 30%		10 35 20%		12.5 42 35%†		7 24* 10%	9.5 21.5 10%	Hykinone on 12th until 18th day
7 5 kg.		12 19 10%		11 25 10%		9.5 24 20%		9.5 13.3 10%		7.5 15.5 10%	10 16 20%	Hykinone on 12th until 18th day
8 4.54 kg.		11 21 10%		10 31 30%		10.5 40 60%		17.5 67 70%†				Hykinone on 12th and 13th days Died on 14th day

* Clotted before $CaCl_2$ added. Results are on cold plasma.
† Icteric plasma
The uppermost figure refers to prothrombin time of whole plasma.
The middle figure refers to prothrombin time of 12.5 per cent plasma.
The lower figure refers to per cent of bromsulphalein retention.
CCl_4—1 c.c./kg. of 50 per cent solution in oil orally.

sidered normal. At the same time (or not more than 24 hours later) estimations of the prothrombin time of whole and diluted (12.5 per cent) plasma were made using the single-stage method of Quick.[3] Plasma protein determinations were carried out by the Barbour-Hamilton falling drop method. The results of the dye retention and prothrombin time are given in the attached table. The initial results were obtained before the first administration of CCl_4.

Analysis of Results

Before the administration of CCl_4, none of the dogs retained as much as 10 per cent of the dye in 30 minutes following the injection. After two doses of CCl_4 dogs 2, 6, and 8 revealed increased retention, dog 3 remaining at the border line. Only dog 6 showed prolongation of the prothrombin time of the whole plasma whereas dogs 2, 3, 4, 6, 7, and 8 disclosed respective increases of the diluted (12.5 per cent) plasma prothrombin time. After the third dose of CCl_4 bromsulphalein retention occurred in all dogs except 3 and 5. The prothrombin time did not show a parallel increase. The undiluted plasma prothrombin time in dog 6 returned to normal and the 12.5 per cent plasma prothrombin time became reduced to normal in dogs 3, 4, and 5. Dogs 2, 6, 7, and 8 showed prolonged prothrombin time. Dog 4 disclosed dye retention but normal prothrombin times, whereas in most of the animals the prothrombin time of the diluted plasma remained increased beyond normal limits although not always directly proportional to the degree of dye retention. It is noteworthy that dogs 6 and 8 showed abnormal retention of bromsulphalein and prolonged prothrombin time of the 12.5 per cent plasma but normal whole plasma prothrombin time. Dog 3 yielded on this day undiluted plasma prothrombin time which was less than those observed during the control periods.

After four CCl_4 injections, dog 2 had already died. Dog 1 revealed normal dye retention and prothrombin time. (It is possible that this animal vomited the last dose of CCl_4.) Dog 3 showed normal dye retention and prothrombin time. This animal showed only a transitory abnormality as revealed by both tests at the time of the third CCl_4 feeding. Dogs 4, 5, 6, and 8 continued to yield abnormal results both in the degree of dye retention and the prothrombin level. Dog 7, however, had less marked dye retention and prothrombin time prolongation than on the previous date.

Hykinone injections were commenced on the day following the fifth and last dose of CCl_4. Four days later dog 8 had succumbed and the surviving animals all showed normal or only very slightly increased retention of dye. The prothrombin times of both whole and diluted (12.5 per cent) plasma became reduced. As noted in the table, spontaneous coagulation of the plasma occurred when the plasma was placed in the constant temperature bath. This took place also in the plasma of dogs 1 and 5, which were not given Hykinone. Because of this phenomenon the prothrombin time had to be estimated using cold plasma and consequently the figures must be accepted with this reservation in mind.

The process appears to have been one of over-compensation in the mechanism of restoration toward normal after the artificially induced prothrombinopenia. A similar condition has been observed in man in the presence of liver disease during recovery from the effects of a small dose of Dicumarol.[4] It has also been noted in multiple myeloma particularly in association with hyperglobulinemia.[12]

In dog 4 the prothrombin time probably continued slightly prolonged. Dog 7 showed recurrence of dye retention 22 days after the initial dose of CCl_4. The prothrombin level was normal at the time and explanation for the phenomenon is wanting. Only in dog 6 was significant prothrombinopenia still evident. It is noteworthy that this animal revealed the most pronounced prolongation of the prothrombin time during the course of the experiment. The plasma protein figures and the results of the blood counts were not in any respect consistent with the other experimental findings and consequently are omitted.

Autopsies were performed on dogs 2 and 8 which died 12 and 16 days after the initial dose of CCl_4, respectively. The liver of dog 2 showed greatly disturbed architecture, granular degeneration and marked fatty infiltration. Evidences of exudation were also visible. Necrosis was not noted. The kidneys revealed cloudy swelling of the tubules, advanced degeneration of the loops of Henle and diffusely distributed areas of early necrosis. The glomeruli were spared. The heart appeared normal.

Dog 8 showed almost identical changes in the liver and in addition hemorrhage within the parenchyma. The kidneys also presented a similar picture with complete obstruction of the lumen of numerous tubules by granular debris. An occasional area of exudation into Bowman's capsule was seen. A mild degree of cloudy swelling was evident in the heart muscle.

Comment

The data presented in the tables giving the combined results of the prothrombin times and bromsulphalein retention should be compared with the findings of Drill and Ivy. These workers used the same means to produce liver damage in dogs but employed a crude method for estimation of the prothrombin time and a thromboplastic agent of low potency. They concluded that estimation of the prothrombin time was a less sensitive test of disturbed hepatic function than bromsulphalein retention.

Our findings, based upon the use of a highly sensitive and constantly reproducible method, yielded the fact that at least after the first few doses of CCl_4, the prothrombin time, as determined by the single-stage procedure (using 12.5 per cent plasma), is as sensitive an indicator of hepatic disturbance as bromsulphalein retention. It appears that generally a rough proportion between the two tests can be demonstrated although in some animals during the later course of the experiments a dissociation is apt to take place. It is of interest that the extent of bromsulphalein retention obtained in the experiments was not as pronounced and constant as in Drill and Ivy's dogs.

After the CCl_4 was withdrawn both tests revealed restoration to normal except dog 6 in which slight prothrombinopenia continued. Increased retention of bromsulphalein 22 days after the initial dose of CCl_4 in dog 7 is without explanation.

The rate of recovery from liver damage was uninfluenced in the four dogs in which Hykinone was administered. This has been noted by others.[5] Hypercoagulability, probably due to over-compensation, was observed irrespective of the use of synthetic vitamin K, during the recovery periods.

These experiments reveal the fact that estimation of the diluted (12.5 per cent) plasma prothrombin time is an important and reliable indicator of early liver damage. The method demands the use of a highly potent standardized thromboplastic agent and carefully controlled technic.

It should be borne in mind that liver damage artificially produced by CCl_4 is not necessarily a true reproduction of the hepatic disorders seen in man. It appears that in man certain forms especially the more acute varieties are, as far as is known, reversible after the toxic agents are withdrawn as was the case in some of the dogs. However, their responses to liver function tests are apt to vary in certain respects from those observed in the dogs, indicating, in such instances at least, that the pathological processes are not identical. This will be illustrated in the data presented below.

Observations in Man

Prothrombinopenia has been found by others in only 53 per cent of cases of liver disease.[6] There is reason to question this figure because of the comparatively low sensitivity of the method used for estimation of the prothrombin time. Accordingly, we undertook a study of the diluted (12.5 per cent) plasma prothrombin time in a series of cases of liver disease. The investigation was extended to include observations on the response to synthetic vitamin K (Hykinone) in large doses in two groups of cases of liver disease: those with normal prothrombin levels and those with prothrombinopenia.

Twenty-three cases constitute the series, including 18 of Laennec's type of cirrhosis of the liver, two of hemachromatosis (diagnosis confirmed subsequently at autopsy), and one of each of the following: acute arsenical hepatitis (examined during the active stage and later when recovery had occurred), metastatic neoplasm of the liver, and macrocytic (pernicious) anemia in a state of remission following liver therapy.

Details of the particular method used for estimation of the prothrombin time have been presented in previous communications.[7, 8] It utilizes the principle of determining prothrombin time in diluted (12.5 per cent) plasma, a procedure shown to be more sensitive than that in which whole plasma alone is used.[9] A standardized thromboplastic agent of high potency is essential for the procedure.

Data

The normal standard diluted (12.5 per cent) plasma prothrombin time was 39.5 seconds. (Standard deviation = 2.5). The variations were within the range of 37–44 seconds. All estimations were done in duplicate.

Serial estimations were made on at least five days during a period of one week to establish the existing level of prothrombin. Synthetic vitamin K (Hykinone) was administered parenterally in dosages of 6 mg. to 20 mg. per day.

For purposes of control six normal subjects were given the identical treatment.

The results in the normals were as follows. The prothrombin time during the first week when no medication was given showed all figures to be within the normal range. Following the administration of Hykinone the prothrombin time became reduced to 36 or 35 seconds for one or two days when it increased to within the normal range, continuing at this level for the duration of the period of observation. One case revealed initially a fall to 29 seconds after which it became elevated to within normal limits (chart 1). One case revealed a sharp rise to 47 seconds for one day from a low figure of 36, following which all of the results continued within the normal range.

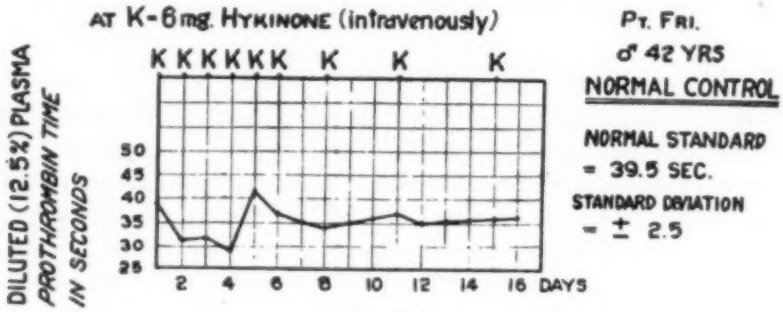

CHART 1.

The cases of liver disease during the control period before menadione was given revealed a remarkable constancy of the level of prothrombin. Of the 23 cases investigated the resting level of prothrombin was normal in only three instances. Twenty disclosed moderate * or marked * prolongation of the prothrombin time. After Hykinone was administered parenterally the cases with established prothrombinopenia showed response patterns as follows: (A) An initial reduction of prothrombin time toward normal for one to three days when it became prolonged to a level in excess of the original figure, followed by a fall to approximately, or slightly below the preëxisting level (chart 2); (B) The prothrombin time remained at about the original level for two or three days when it became increased for two or three days and gradually receded to or slightly less than the original figure (chart 3); (C) Where the resting level of prothrombin was normal, after the third or fourth day of menadione medication the prothrombin time increased slightly at which figure it remained for a few days when it returned to normal again (chart 4).

* Moderate = between 1½ and twice normal.[4]
Marked = approximately twice normal.

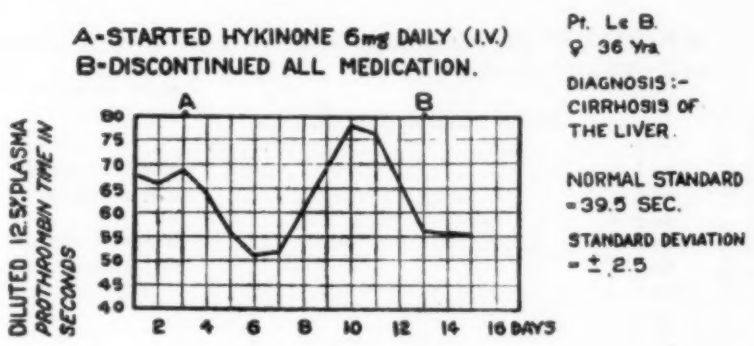

CHART 2.

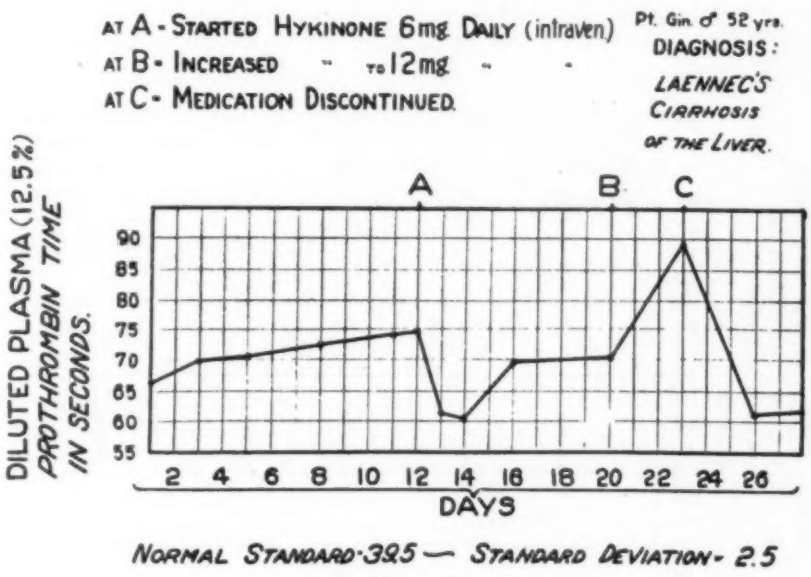

CHART 3.

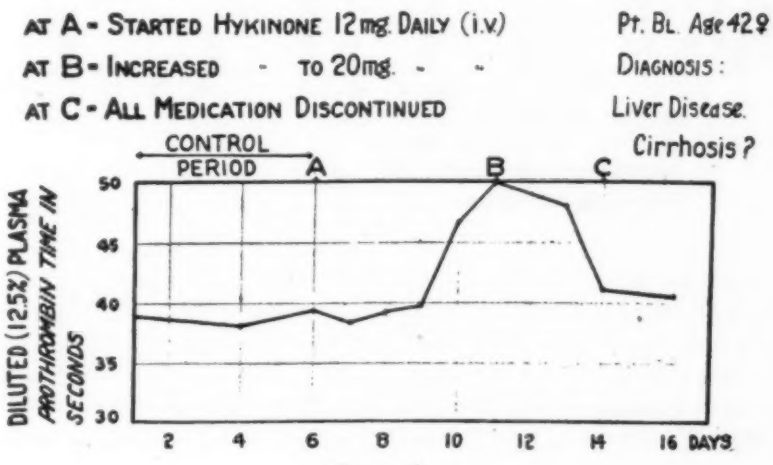

CHART 4.

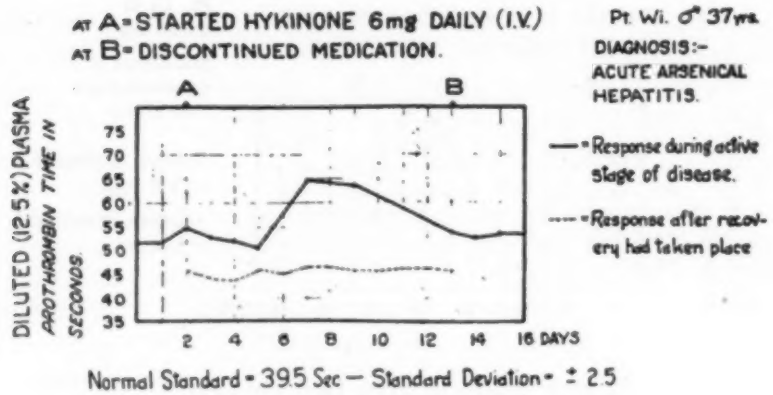

CHART 5.

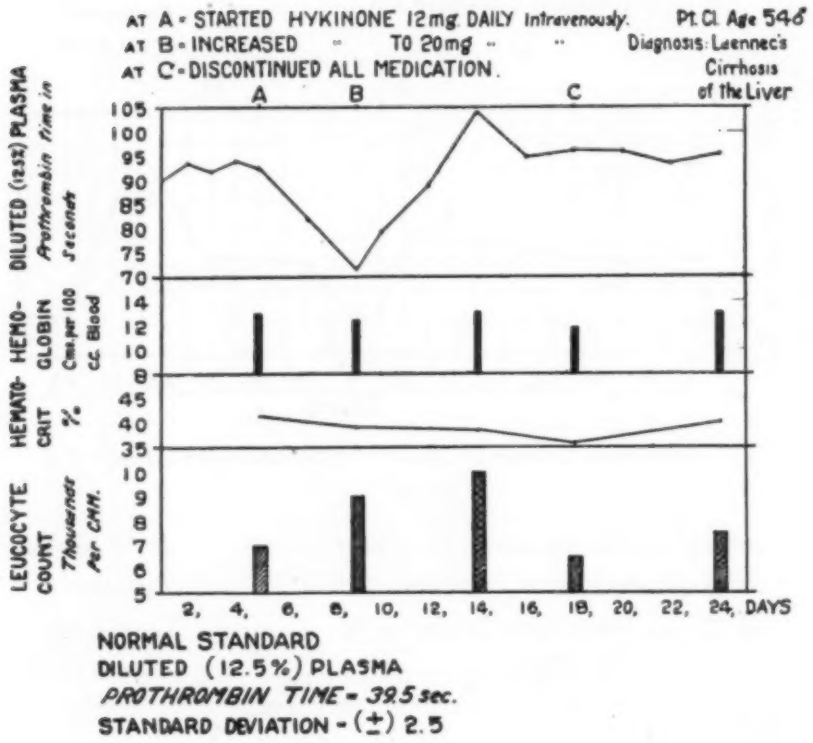

CHART 6.

Attempt was not made in every case to compare the findings with other liver function tests. We attempted primarily to determine the prothrombin time in the presence of liver damage. It is worthy of especial note, however, that in four instances (i.e., the three cases in which the prothrombin levels were normal and one case of hemachromatosis and refractory anemia which

on section showed fatty degeneration of the liver lobules) deviation of the prothrombin curves from the normal after Hykinone was in each case the only abnormality in liver function detected clinically. The bromsulphalein retention was not abnormal in any of these four cases, and only one revealed abnormal cephalin flocculation.

Analysis of Results

The data herein described indicate that under the conditions presented the system for elaborating prothrombin functions at a constant and apparently maximum level. In the presence of normal function additional stimulation by vitamin K serves to augment the activity. This continues for only a short transitory interval after which the tempo of prothrombin elaboration returns to the normal initial rate despite the continued administration of menadione. In the presence of liver damage with existing normal prothrombin levels, the persistent stimulation induced by repeated parenteral administration of synthetic vitamin K appears temporarily and partially to exhaust the prothrombin system for a few days when it recovers its normal rate and continues at this level.

Where prothrombinopenia had already been established in liver disease, the response to large doses of antihemorrhagic substance reveals an inability to revert to normal. This has previously been reported by earlier observers.[10] The tendency toward temporary and partial exhaustion of the prothrombin mechanism was decidedly more pronounced in such cases than in those with normal initial prothrombin levels. An analysis of data presented by previous authors has revealed comparable responses, although the phenomena seem to have attracted no especial interest.[11, 13]

It is noteworthy that the case of acute arsenical hepatitis yielded the reaction of liver damage during the active stage and showed a normal response after recovery had taken place (chart 5).

Emphasis is placed upon the findings in four cases in which other procedures including bromsulphalein retention were normal and in which pathologic prothrombin curves constituted the only laboratory demonstration of liver disease.

Initial prothrombinopenia was found in 20 of our series of 23 cases of liver disease.

Discussion

We find, as have previous authors,[3, 10, 11, 13] that in the presence of liver disease an established prothrombinopenia cannot be restored to normal by the administration of synthetic vitamin K. Such a sequence of changes portends liver disturbance (unless other explanations are discovered).

The sensitivity of the prothrombin estimations is markedly increased by the use of diluted (12.5 per cent) plasma. It accounts for our finding pro-

thrombinopenia in a much higher proportion of cases than others using whole plasma.*

The following procedure is suggested as a means of establishing the presence of hepato-cellular pathology: the resting level of diluted (12.5 per cent) plasma prothrombin time is determined. Synthetic vitamin K is given parenterally daily for about one week. If prothrombinopenia is present and it fails of correction after menadione, liver disease is presumed to be responsible. Restoration to a normal prothrombin level indicates adequate hepatic function. Where the resting prothrombin time is normal and it becomes prolonged after several administrations of menadione (the increased prothrombin time lasts for two or three days) hepatic disturbance should be considered the cause, unless other reasons are revealed. We have observed it in man only in the presence of liver damage.

On the question of the relative sensitivity of the various liver function tests the data herein presented indicate that the estimation of the diluted (12.5 per cent) plasma prothrombin time and the response to parenteral menadione is no less sensitive than bromsulphalein retention. Actually, in four cases of liver disease we found the prothrombin curves to be superior to bromsulphalein retention or cephalin flocculation in revealing hepatic damage.

By virtue of its chemical constitution menadione is apt to cause hemolytic anemia. In other series of experiments to be published separately we shall describe the effects in animals of doses many times in excess of those administered in our investigations in man. The findings indicate that after huge doses there can be produced regularly an anemia characterized by a fall in hemoglobin and erythrocytes and occasionally the appearance of normoblasts in the circulating blood. Upon withdrawal of the quinone there follows a prompt return to a normal blood picture. In the above experiments in man we noted anemia only rarely and when it did arise it was always mild; and in every case a return to the normal blood picture occurred promptly after the withdrawal of the Hykinone (chart 6).

Summary

In dogs, following the administration of CCl_4, the prothrombin time of diluted (12.5 per cent) plasma was found to be as sensitive an indicator of hepatic disturbance as bromsulphalein retention.

Generally a rough correlation between the two tests was demonstrated. Later in the course of the experiments a dissociation of the procedures occurred.

The rate of recovery following the withdrawal of CCl_4 was uninfluenced by the administration of synthetic vitamin K.

In man, prothrombinopenia as determined by estimation of the diluted

* Advanced renal disease, especially with azotemia, appears to augment the prothrombin level. (Possibly prothrombin is eliminated by the kidneys.)

(12.5 per cent) plasma prothrombin time was demonstrated in 20 out of 23 cases.

Following repeated parenteral administration of 6 to 20 mg. of Hykinone almost daily, characteristic curves of the prothrombin response were observed in normals and in cases of liver disease both with preëxisting prothrombinopenia and with normal resting levels of prothrombin.

Deviations from the normal in response to synthetic vitamin K were found to occur in instances of liver disease where bromsulphalein retention and cephalin flocculation were normal.

The findings were obtained by the estimation of diluted (12.5 per cent) plasma prothrombin time.

Repeated administration of large doses of menadione was found to cause anemia which returned to normal promptly upon withdrawal of the antihemorrhagic substance.

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LIVER DYSFUNCTION HYPERGLYCEMIA: ITS ETIOLOGY AND RELATION TO DIABETES MELLITUS*

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Recent work has shown that numerous conditions other than diabetes mellitus are accompanied by hyperglycemia; the more significant of these conditions include obesity, liver damage, and hyperpituitarism. That this symptom appears in such diverse diseases is explicable by the fact that control of the blood sugar is determined not only by the level of insulin in the blood but by the state of the liver, kidneys and gastrointestinal tract as well as by the level of the pituitary-adrenal hormones.

Observations

While engaged in testing a modified insulin preparation in a series of diabetic patients, the authors felt obliged to ascertain directly the severity and definiteness of the disease in each case. This was done by keeping the patient on his regular hospital diet but withholding insulin for 24 to 48 hours. Blood sugars were run at regular intervals (four to eight hours) and urine samples were checked for sugar and acetone every four hours. At the end of the experimental period the patients were brought back under control with suitable doses of regular insulin.

This work brought to our attention very forcefully the considerable differences between the two major classes of diabetes mellitus patients: the adult and juvenile diabetics. The results obtained in two representative cases are shown in table 1. Differences just as marked are noted when (a) the onset and course and (b) the response to treatment of these two types of diabetics are considered. These may be summarized as follows.

(a) *Onset and course.* Juvenile diabetics (i.e., patients suffering from insulin deficiency) are generally first observed in a very acidotic or precomatose condition. Characteristically, they give a history of polyuria and polydipsia for about a month with polyphagia and weight loss for an even longer time. When the patient has marked complaints, sugar and acetone are always found in the urine and an acidosis, hypercholesterolemia, hyperglycemia and dehydration are not infrequent. Unless treated by insulin they progress rapidly to coma and death. But given an adequate diet and insulin, they soon show excellent clinical condition.

On the other hand, most "adult diabetics" (hepatic dysfunction hyperglycemics) show no such extreme course, but are generally picked up on a

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From the medical service of Dr. Samuel J. Taub, Ward 55, Cook County Hospital.

routine examination of the urine which very often shows sugar but rarely acetone. Polyuria, polydipsia, polyphagia, and weight loss are only sporadically found. The chief findings are glycosuria, hyperglycemia and certain changes in the blood picture characteristic of low grade liver damage. The onset of the disturbance is late in life and it frequently involves obese individuals. The authors, among others, have found that lack of insulin treatment gives no increase in the symptoms over a long period of time. Many of these cases show spontaneous remission of the glycosuria for no apparent cause.[1, 2, 3]

TABLE I

Effect of Withholding Insulin from Adult and Juvenile Diabetics

Hours	Case 1			Case 2		
	Blood Sugar mg. %	Urine		Blood Sugar mg. %	Urine	
		Sugar	Acetone		Sugar	Acetone
0	111	0	0	218	+	0
4	119	0	0	243	+	0
8	164	0	0	269	++	0
12	292	+++	0	261	+++	0
16	344	++++	0	248	+++	0
20	395	++++	0	227	++	0
24	419	++++	0	213	++	0
28	442	++++	0	—	+	0
32	—	++++	0	274	++	0
36	438	++++	0	—	+++	0
40	—	++++	0	251	+++	0
44	450	++++	+	—	+++	0
48				208	+	0

Case 1: A white male, 32 years old, who had been a diabetic for 20 years. He was controlled on 65 units of protamine zinc insulin and 15 units of regular insulin administered together every morning.

Case 2: A white male, 56 years old, who had been diagnosed as diabetic six years previously. He was given a morning dose of 15 units of regular insulin daily.

Both patients were maintained on a normal hospital régime during the experiment. Zero time in the table represents 7:00 a.m., the usual hour for the daily insulin injection. During the experiment no insulin was administered, the last dose having been given 24 hours before zero time. Feedings were at 7:30 a.m., 11:30 a.m., and 5:00 p.m., with a snack at 9:00 p.m. before retiring. Lunch was the largest meal of the day.

(b) *Treatment.* The juvenile type has a moderate to high insulin requirement, shows a good response to protamine zinc insulin, and gets along well on a moderate carbohydrate diet (180–350 C, 100 P, 60 F). The "adult type" requires only low to moderate insulin dosages and, in general, is quite sensitive to regular insulin but responds poorly to protamine zinc insulin. We have found that these hyperglycemic adults show greater improvement on a high to very high carbohydrate diet than when one low to moderate in carbohydrate is prescribed.[1, 3]

These differences are so considerable that we were forced to the conclusion that a fundamental difference existed between these two types of diabetics and that rather than suffering from variants of the same disease, two different diseases showing similar symptoms were existing side by side.

The following facts led us to take the stand that the large majority of adult hyperglycemics, that is, individuals developing hyperglycemia after the third decade, were suffering from low grade liver damage rather than the insulin deficiency implied in a diagnosis of diabetes mellitus.

(*a*) The liver is the organ responsible for regulating the blood sugar.

(*b*) Disturbances of liver function would be expected to cause alterations in the carbohydrate regulation of a certain number of cases and, indeed, this has already been shown to be the case by other investigators.[4, 5, 6, 7, 8, 9, 10]

(*c*) Adult diabetics are almost exclusively people in the fourth decade or older, a time when low grade liver dysfunction would be much more prone to appear than in younger people.

(*d*) In the patients we observed many of the adult diabetics had a history of excessive alcoholism and poor diet.

(*e*) Most important, all cases of adult diabetics which we rediagnosed as liver dysfunction hyperglycemics showed evidences in their blood chemistry of subclinical or low grade liver disease.

Consequently, our treatment of these individuals was altered. In many instances, these cases were treated as pure liver disease patients, insulin being withheld and therapy consisting of a high carbohydrate, high protein and low fat diet. These people have in the great majority of cases shown a pronounced improvement in their "diabetic" symptoms. In the cases where no concomitant insulin deficiency existed (this group includes about 80 per cent of the adult "diabetics" in our experience) there was never in any case an increase in the extent of the hyperglycemia or a more marked impairment of the glucose tolerance even though no insulin was administered. Although the proportion of "adult diabetics" with pure liver disease is large, there still are many who possess either a relative or an actual insulin deficiency together with their liver disease. This may be due to degenerative changes in the pancreas or to associated disease in the other endocrine systems. However, these deficiencies are generally mild, and the patients are best treated with small dosages of insulin and high carbohydrate diets.[2, 3, 11]

As a result of daily experience, we have taken the stand that in those adults whose hyperglycemia becomes manifest late in life (after the third or fourth decade), management should be directed against the primary disease, usually liver damage, and not against the symptom, hyperglycemia. The physician is then faced with the problem of determining whether he is dealing with a case of pure liver damage, pure diabetes or a mixture of both liver disease and insulin deficiency. This is a difficult problem, especially since as has been emphasized above, the majority of "adult diabetics" are only subclinical liver disease patients and as such are not easily recognized. However, these obstacles can be partly minimized by the use of certain simple and readily available laboratory tests.

The following procedure has been found most satisfactory. (1) A complete series of blood chemical tests should be made to discover if any deviations characteristic of liver deficiency exist. This should include determina-

tion of total protein, albumin-globulin (A/G) ratio, non-protein nitrogen (N.P.N.), uric acid, cholesterol and cholesterol esters, and one of the serum precipitation tests (Takata-Ara, colloidal gold, etc.). (2) Some of the standard dye elimination tests and hippuric acid synthesis, etc. (3) The intravenous glucose-tolerance test. As Soskin has demonstrated, many liver cases give an intermediate curve between normal and the severely diabetic.[10] If this is found, it is significant; but we have on record a number of unquestioned cases of liver disease who give a very severe diabetic type of response. It should be remembered that in liver disease, all liver functions including the ability to regulate the blood glucose may sustain any degree of impairment from mild to severe. The use of any one test alone gives anomalous results and makes accurate diagnosis of liver dysfunction impossible.

Other diagnostic criteria are found in the history and the character of response to therapy. As emphasized in the early part of this paper, one should be most reluctant to make a diagnosis of diabetes mellitus in an elderly individual who does not give the typical onset and course of juvenile diabetes and who has a history of inadequate diet or repeated exposure to such hepato-toxic agents as alcohol, or both. The response to various types of insulin control is significant. A high sensitivity to regular insulin with a poor response to protamine zinc insulin is characteristic of the cases of liver disease. These respond excellently to a high carbohydrate diet without insulin. They spill no more sugar on a high than on a low carbohydrate diet, and their blood sugars are not significantly increased by the high carbohydrate therapy. Of major importance is the response of the patient to high carbohydrate, no insulin therapy; the maintenance of an excellent clinical condition and the improvement thereof over a fair period of time indicate unequivocally the absence of actual insulin deficiency. These observations, correlated with the previous laboratory tests, will make possible the correct evaluation of the patient's status.

Similar conclusions have been reached by Newburgh in his work on "obese diabetics."[2] He observed the same symptomatology which we had noted in our "adult diabetics" and found that the most important therapy in these cases was reduction of the individual's weight. In most cases a lessening of the individual's obesity was accompanied by a marked increase in his glucose tolerance. Newburgh's conclusion was that although the cause of the disturbance in these individuals is obscure, they are not suffering from diabetes. Boyd[12] has suggested that the difficulty in these cases may be caused by an infiltration of the liver with fat. In these cases where the caloric intake must be kept low, we merely adjust the diet to give the patient a high carbohydrate-fat ratio, provided there is no acidosis.

The patient who displays evidence of liver damage and a moderately good response to protamine zinc insulin may be considered as having an associated mild insulin deficiency, and may be treated with a high carbohydrate diet and moderate insulin dosage. However, in no such case should the emphasis be placed upon the maintenance of a sugar-free urine; one should stress,

rather, the treatment of the liver condition. The major criterion of the treatment should be the patient's clinical status.

The scheme of diagnosis and treatment outlined above is not merely theoretical. Its clinical application has met with considerable success for over a year in our work at Cook County Hospital. This is shown in the cases detailed below.

Case Reports

Case 1. D. G., a white male, aged 50 years, came to the hospital with complaints of extreme progressive fatigue for the preceding three years and of diabetes mellitus for the preceding 10 years. This patient had never taken insulin, but was on a strict, low carbohydrate diet. Physical examination revealed the presence of a double mitral murmur, but no other abnormalities, and no evidence of cardiac decompensation. The hematologic picture was within normal limits. Urinalysis revealed a 4 plus test for sugar, negative test for acetone, albumin, and was negative microscopically. The specific gravity of the urine was 1.020. Blood chemistry: Total proteins, 6.6 gm. per cent; albumin, 3.6 gm. per cent; globulin, 3 gm. per cent; uric acid, 9 mg. per cent; cholesterol, 200 mg. per cent; cholesterol esters, 68 per cent; creatinine, 2 mg. per cent; non-protein nitrogen, 48 mg. per cent. The fasting blood sugar varied on successive days from 110 to 290 mg. per cent. The Exton-Rose glucose tolerance test, after a three day high carbohydrate diet, was: fasting, 290 mg. per cent; ½ hr., 270 mg. per cent; 1 hr., 250 mg. per cent. An intravenous glucose tolerance test was: fasting, 110 mg. per cent; ½ hr., 220 mg. per cent; 1 hr., 220 mg. per cent; 2 hr., 100 mg. per cent. The patient's complaint was diagnosed as liver dysfunction hyperglycemia and he was placed on a diet of carbohydrate, 450 grams; protein, 110 grams; fat, 65 grams. He was also given vitamin B complex and choline chloride, two grams per day. Fatigue disappeared soon after the onset of therapy and the patient became more active in his business than he had been in the past 10 years. His subjective condition was excellent. After 14 months of therapy, the total proteins were 6.2 gm. per cent; albumin, 4.2 gm. per cent; globulin, 2.6 gm. per cent. There was no more glycosuria. The intravenous glucose tolerance was essentially unchanged.

Case 2. G. L., a white male, aged 55, came into the hospital complaining of uncontrolled diabetes and a sensation of weakness. The patient had been diagnosed as a diabetic 10 years previously and placed on a low carbohydrate, high fat diet without insulin. At that time he was very obese, weighing 270 pounds. He also gave a history of excess alcoholism of many years' duration. During the intervening 10 years the patient continued drinking, although more moderately. Physical examination revealed slightly icteric sclerae and an irregularly nodular liver, palpable three fingers below the costal margin. The essential findings in the urine were a 4 plus test for sugar and an occasional trace to one plus test for acetone. Hematologic picture was normal. Blood chemistry: total proteins, 5.8 gm. per cent; albumin, 2.3 gm. per cent; globulin, 3.5 gm. per cent; non-protein nitrogen, 46 mg. per cent; icterus index, 14; total cholesterol, 150; Takata-Ara test, 4 plus. An intravenous glucose tolerance test, after three days on a high carbohydrate diet, was: Fasting, 350 mg. per cent; ½ hr., 430 mg. per cent; 1 hr., 397 mg. per cent; 2 hr., 340 mg. per cent; 3 hr., 326 mg. per cent. A diagnosis of liver dysfunction hyperglycemia was made. The diet ordered was: carbohydrate, 450 grams; protein, 110 grams; fat, 60 grams. He was also given vitamin B complex and choline chloride, two grams daily. Marked subjective improvement occurred rapidly, and no acetone could be found in any urine sample. Eight months later the total proteins were: 6.0 gm. per cent; albumin, 3 gm. per cent; globulin, 3 gm. per cent. The urine showed a two plus test for sugar, no acetone. Icterus index was 4.

Case 3. S. T., a white male, aged 40, was admitted to the hospital in coma, with an admission diagnosis of diabetic coma. Physical examination revealed a hard, nodular liver, palpable four fingers below the costal margin, and a moderate papilledema. The catheterized urine sample was 4 plus for sugar and negative for acetone. A history was obtained from his wife. Six months previously this patient had been diagnosed as having diabetes mellitus and was placed on a diabetic diet without insulin. He had continued uneventfully until one day before admission, when he collapsed at work. A physician had administered 180 units of regular insulin prior to admission. Further questioning revealed that the patient had been a heavy alcoholic for the past 20 years. A diagnosis was made of severe portal cirrhosis with cerebral edema. The therapy instituted was continuous infusion of 10 per cent glucose in saline. The temperature gradually rose, and 24 hours after admission the patient died. Blood chemistry reports showed a CO_2 combining power of 44 volumes per cent; total proteins were 6.0 gm. per cent; albumin, 2.1 gm. per cent; globulin, 4.9 gm. per cent. Blood sugar on admission was 194 mg. per cent. The urine at no time showed more than traces of acetone. Autopsy showed hemachromatosis of the liver and pancreas, severe portal cirrhosis of the liver, and acute focal necrosis within the liver. The pathologist's opinion was that the cause of death was the acute focal necrosis of the liver.

Case 4. J. S., a white male, age 65, was admitted to the hospital with a diagnosis of arteriosclerotic heart disease and diabetes mellitus. Physical examination revealed left heart enlargement; the left heart border was in the left axillary line in the sixth interspace. There was a harsh systolic murmur at the apex and parasternal border. The liver was palpable, and non-tender. An electrocardiogram showed evidence of left axis deviation and coronary sclerosis. The blood pressure was 195 mm. Hg systolic and 110 mm. diastolic. The urine was negative except for a 4 plus test for sugar. This patient had been on a dosage of protamine zinc insulin, 20 units daily for the past five years, since the date of onset of his diabetes. The patient complained of many attacks of chest pain coincidentally with insulin reactions. Blood chemistry: total proteins, 5.0 gm. per cent; albumin, 2.4 gm. per cent; globulin, 2.6 gm. per cent; non-protein nitrogen, 40 mg. per cent. Diagnosis: Hypertensive heart disease and liver damage. Therapy was a diet of carbohydrate 350 grams, protein 100 grams, and fat 60 grams. No insulin. Vitamin B complex was administered. Glucose tolerance test (Exton-Rose) on admission was: fasting, 177 mg. per cent; ½ hr., 249 mg. per cent; 1 hr., 220 mg. per cent. Eight months later the fasting blood sugars varied from between 100 mg. per cent to 150 mg. per cent, and there had been marked subjective improvement over those months. No change in the plasma proteins was observed.

Case 5. H. K., a white male, aged 85 years, was admitted to the hospital with a diagnosis of decompensated arteriosclerotic heart disease and diabetes mellitus. In the history, it was noted that the patient had been diabetic for the past 35 years and had been taking 20 units of insulin daily for the past 18 years. The patient was digitalized and rapidly compensated. Insulin was stopped. Fasting blood sugars varied from 162 to 204 mg. per cent. The total proteins were 5.1 gm. per cent; albumin, 2.4 gm. per cent; globulin, 2.7 gm. per cent; non-protein nitrogen, 45 mg. per cent. Urinalysis showed a 4 plus test for sugar and was negative for acetone. The treatment instituted was a diet of carbohydrate, 350 grams; protein, 80 grams; fat, 55 grams. Vitamin B complex was given, but no insulin. Thirteen months after admission his condition was good. No essential changes in the blood sugar or plasma proteins had occurred. There was never any acidosis.

Case 6. J. T., white male, aged 54, came into the hospital for investigation of his "diabetes," which had just been discovered on routine analysis by a physician treating a "sore on the toe." This patient felt well and had come in only because the

physician told him his diabetes should be investigated. Physical examination was essentially negative. Blood chemistry was within normal limits except for plasma proteins: total proteins, 6.8 gm. per cent; albumin, 3.2 gm. per cent. Globulin, 3.6 gm. per cent. An intravenous glucose tolerance test was: fasting, 172 mg. per cent; ½ hr., 230 mg. per cent; 1 hr., 220 mg. per cent; 2 hr., 175 mg. per cent; 3 hr., 169 mg. per cent. Diagnosis was made of liver dysfunction hyperglycemia. Therapy consisted of a diet of carbohydrate, 475 grams; protein, 110 grams; fat, 70 grams. Vitamin B complex and choline chloride, two grams daily, were given. The patient felt well on this régime. Ten months later fasting blood sugars varied from 70 mg. per cent to 182 mg. per cent. There were no essential changes in the protein values.

Case 7. L. M., white male, aged 51, was found to have sugar in the urine and was referred for study. There were no subjective complaints. Physical examination was essentially negative. Blood chemistry was: total proteins, 7.0 gm. per cent; albumin, 4.0 gm. per cent; globulin, 3 gm. per cent; non-protein nitrogen, 38 mg. per cent; total cholesterol, 175 mg. per cent; esters, 60 per cent; Takata-Ara two plus. The fasting blood sugar was 205 mg. per cent. An intravenous glucose tolerance test showed: Fasting, 187 mg. per cent; ½ hr., 234 mg. per cent; 1 hr., 209 mg. per cent; 2 hr., 195 mg. per cent; 3 hr., 201 mg. per cent. Diagnosis of liver dysfunction hyperglycemia was made. Treatment ordered was a diet of carbohydrate, 475 grams; protein, 100 grams; fat, 65 grams; vitamin B complex was also given. This patient was watched for nine months, at the end of which time he was still feeling fine and was without subjective complaints. Fasting blood sugars varied from 120 mg. per cent to 173 mg. per cent. Glycosuria was minimal.

Case 8. J. R., colored male, 57 years of age, was admitted to the hospital because of uncontrolled diabetes mellitus. This patient gave a history of having had diabetes mellitus for two years. He was on a diet and 25 units of protamine zinc insulin per day, but on this régime the patient would have reactions in the late afternoon, and would still find sugar in his urine in the mornings. Physical examination revealed a palpable liver but was otherwise negative. Blood chemistry: total proteins, 5.2 gm. per cent; albumin, 3.3 gm. per cent; globulin, 1.9 gm. per cent; non-protein nitrogen, 30 mg. per cent; cholesterol, 150 mg. per cent. The cephalin flocculation test was two plus. Intravenous glucose tolerance test, after three day preparation with high carbohydrate diet and no insulin: fasting, 155 mg. per cent; ½ hr., 208 mg. per cent; 1 hr., 200 mg. per cent; 2 hr., 183 mg. per cent. Urinalysis showed a 4 plus test for sugar, but negative tests for acetone. A therapeutic diet of carbohydrate, 400 grams; protein, 100 grams; fat, 60 grams was ordered. Vitamin B complex was also ordered. All insulin was discontinued. The patient felt very well, and very much appreciated the absence of insulin reactions. Six months after the onset of therapy, the total proteins were 6.1 gm. per cent; albumin, 4 gm. per cent; globulin, 2.1 gm. per cent; cholesterol was 165 mg. per cent. The blood sugars and glucose tolerance tests were essentially unchanged. There was no increase in the glycosuria and there was never any acetone in the urine.

Case 9. S. S., aged 64, white male, came into the hospital with complaints of dizziness and weakness for six months, and of diabetes mellitus for nine years. Physical examination revealed a blood pressure of 240 mm. Hg systolic and 120 mm. diastolic, a markedly enlarged left heart, to the anterior axillary border in the seventh interspace, a rough harsh systolic murmur at the apex, and a grade four hypertensive neuroretinopathy in the fundi. There were many coarse râles throughout the lungs. The urine showed heavy albumin, red cells, casts, and sugar. The specific gravity varied between 1.010 and 1.015. The non-protein nitrogen was 110 mg. per cent; total proteins, 4.0 gm. per cent; albumin, 2.2 gm. per cent; globulin, 1.8 gm. per cent. The blood sugars varied from 130 mg. per cent to 247 mg. per cent. The patient had previously been on an insulin dosage of 40 units of regular insulin daily. This was

stopped, and intravenous glucose and fluids were given. The blood sugars fell to fasting levels of 111 mg. per cent to 137 mg. per cent. At no time was there acetone in the urine. After two months, the patient succumbed in uremic coma. There were never any signs of a diabetic type of ketosis.

Case 10. K. T., a white male, aged 48, came into the hospital with uncontrolled diabetes and bilateral inguinal hernia. Surgery was requested. This patient had been diagnosed as a diabetic 12 years previously, and had been placed on a low carbohydrate diet and given 40 units of protamine zinc insulin daily. Urinalysis, on admission, showed sugar, 4 plus; acetone, 4 plus; albumin and microscopic negative. Blood count was negative. Admission blood sugar was 365 mg. per cent. Total proteins were 4.3 gm. per cent; albumin, 1.9 gm. per cent; globulin, 2.4 gm. per cent; non-protein nitrogen 45 mg. per cent; total cholesterol 279 mg. per cent; esters 56 per cent. Physical examination was negative except for the presence of the bilateral inguinal herniae. The patient was originally given a diet of carbohydrate, 120 grams; protein, 60 grams; and fat, 70 grams. Thirty units of regular insulin were injected three times a day, before meals. On this régime, hyperglycemia, acidosis and weight loss continued unabated. At this point the authors were called in. A diagnosis was made of diabetes mellitus with associated liver damage. The diet was changed to carbohydrate, 400 grams; protein, 110 grams; fat, 70 grams. Vitamin B complex was given. Regular insulin, units 25, t.i.d., a.c., and 15 units of regular insulin at bed-time with 10 ounces of orange juice were ordered. The blood sugars fasting and after meals dropped to normal; the acidosis disappeared. The patient gained weight and marked subjective improvement occurred. The insulin was then changed to protamine zinc insulin, units 60, and regular insulin, units 30, every morning in different sites. Fasting blood sugars ranged from 90–115 mg. per cent. The total proteins rose to 6.2 gm. per cent; albumin, 3.4 gm. per cent; globulin 2.6 gm. per cent. Patient was ready for surgery. The operation was performed and the patient had an uneventful recovery.

Discussion

Hyperglycemia and glycosuria have long been recognized as findings in such conditions as head injuries, the pneumonias, severe toxemias, and chromaffin tissue tumors. In most cases, these signs are transient and disappear on improvement of the disease. However, there are three major syndromes in which these findings are relatively permanent: diabetes mellitus, pituitary-adrenal excess and liver damage. Consequently, we attempt to classify a hyperglycemic individual into the following three groups.

(*1*) *Actual insulin deficiency.* This is due to malfunction of the islets of Langerhans in the pancreas. Here, insulin must be given. Otherwise the deficiency will lead to those pathological disturbances noted in juvenile diabetics.

(*2*) *Relative insulin deficiency.* This is due primarily to an excessive production of those hormones of the pituitary and adrenals which regulate carbohydrate metabolism. Since these hormones operate mainly as a counter-balance to insulin, their relative excess causes hyperglycemia and increased gluconeogenesis with ketosis. This results in a clinical picture which resembles the earlier stages of a true diabetes mellitus.

Administration of insulin corrects this imbalance and results in the disappearance of the "diabetic" symptoms. However, there is no actual insulin

deficiency, and even if exogenous insulin is not administered, these patients show no severe symptoms, coma or death.

(*3*) *Hepatic insufficiency.* This has as one of its most frequent manifestations an inability properly to regulate the blood sugar. We have found that a majority of the adult "insulin-insensitive" diabetics are not true diabetics at all but are cases of liver injury showing hyperglycemia as one of the indications of their hepatic dysfunction. The outstanding findings in these individuals are:

a. a vacillating blood sugar level, generally higher than normal; running on the average about 200 to 250 mg. per cent,
b. a diabetic or semidiabetic glucose tolerance curve,
c. a normal blood level of acetone bodies in well nourished patients,
d. alterations in the blood values of uric acid, non-protein nitrogen, total protein, A/G ratio, cholesterol and cholesterol esters, and bilirubin.*

The authors offer the following explanation for these findings. All functions of the liver are mediated by enzyme systems which in themselves are very complex and through which the original components of food are serially processed.† Any deficiency of one or more of the crucial components of these enzyme systems will lead to functional breakdown of the whole serial chain. Adding excesses of non-deficient components will at most effect only a slight overall improvement since no increase in the quantity of limiting factor has been made. In liver damage, a dysfunction of the enzyme systems regulating the blood sugar is as probable as, and indeed is frequently concomitant with, one in the systems regulating other liver functions such as the plasma protein. Since the enzymes controlling the level of the blood sugar and those involved in converting blood glucose to liver glycogen and the reverse are intimately related, one would expect any dysfunction in these systems to be represented by both a hyperglycemia and impaired glucose tolerance. This would mean that ingested glucose would be handled less adequately and more slowly, and that the equilibrium level of glucose in the blood would be set up higher than normal. However, since the deficiency in these systems is not in the amount of insulin present but rather resides in some other limiting component (such as in the actual concentration of an enzyme), administration of the hormone has a relatively small effect on the blood sugar level or glucose tolerance. The systems involved in the metabolism of fat are generally not particularly impaired and since there is no demand for really excessive glucose production

* Facilities for running the common dye-excretion tests were not available at Cook County Hospital.

† For example, the conversion of glucose to glycogen in the liver involves one of these complex enzyme systems rather than a simple enzymatic reaction. The glucose must first be phosphorylated and the phosphorylated units then combined into glycogen. The source of the phosphorylating material is energy-rich phosphate compounds which are in turn generated by the oxidation of the products of intermediary carbohydrate metabolism.[13]

by the liver, no overproduction of acetone bodies is initiated. The alterations in other blood constituents found in this condition are merely indications of the functional breakdown of other liver enzyme systems.

Therefore, since no actual or relative deficiency exists, insulin is not indicated in these individuals. Although a dose of regular fast-acting insulin may overpower the impaired systems and bring the blood sugar down temporarily, no slow-acting insulin will achieve this result. The liver damage does not affect the gluconeogenic systems in such fashion that overproduction occurs. Indeed, if the damage is severe, the reverse may be true. Ketosis may result only if the glucose loss in the urine is so great and dietary carbohydrate so small that gluconeogenesis must proceed at an excessive rate to maintain the blood sugar. Therefore, in these cases insulin plays no part in therapy and may cause harm upon continued administration.* The proper therapy is a high carbohydrate diet (400–800 grams) which (*a*) in itself has a restorative effect upon the liver parenchyma and (*b*) reduces the work of the liver in supplying carbohydrate lost to the body in the urine.

Summary

1. "Adult" diabetics are shown to differ so markedly from the juvenile type that they are considered as suffering from a distinctly different disease.

2. The dysfunction in the majority of adult diabetics seen by us is demonstrated to be hepatic rather than pancreatic in origin.

3. Therapy directed toward the liver is shown to give far greater success in the management of these patients than insulin administration and a diabetic régime.

We wish to express our gratitude to Dr. Hugo Fenske, Dr. Arthur Zweibel and Dr. Jack Rodriquez for assistance rendered us in the course of this investigation.

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* It has been reported that excessive insulin administration has led to islet atrophy in rats.[14] But even more important is the effect of excess insulin administration upon the deposition and mobilization of glucose. Soskin has shown that the presence of extra insulin in the blood causes (*a*) an increased deposition of glycogen in the peripheral tissues and (*b*) a reduction in the amount of glycogen stored in the liver.[15] This has the effect of reducing the blood sugar level. Furthermore, it causes a redirection of administered glucose away from the liver toward the peripheral tissues. If this carbohydrate is being given to make up for glucose lost in the urine, simultaneous administration of insulin in great measure defeats one's purpose since a large portion of the glucose is converted into non-labile muscle glycogen and the needed replacement glucose must still be formed by the gluconeogenic systems of the liver. In liver damage where a high blood sugar is a necessary part of the therapeutic routine, this is an especially serious effect. The clinical validity of these conclusions is shown by the experiments of Rosenbaum et al., who found that the administration of insulin to normal individuals caused them to show a diabetic glucose tolerance curve for several days indicating that the capacity of the liver to store glucose was definitely below par.[16, 17, 18]

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CASE REPORTS

PENICILLIN IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS; REPORT OF CASE *

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The effectiveness of penicillin in the treatment of subacute bacterial endocarditis is now under investigation at various centers. Early trials with small amounts of the drug, although discouraging, indicated its ability to sterilize the blood stream temporarily in some instances. The National Research Council [1] reported disappointing results in 17 cases in which the total dosage varied from 240,000 to 1,760,000 Florey units administered over a period of from nine to 26 days. Herrell [2] was unable to influence the course of one case in which the organism was inhibited (in vitro) by penicillin in dilutions of 1:500,000. The total dosage employed, however, was only 128,000 units and the duration of therapy only six days. Herrell observed the reappearance of *Streptococcus viridans* in the blood within four to six hours after administration of penicillin was discontinued. He emphasized that although the blood stream may be temporarily freed of organisms, the persistent focus on the heart valve precludes the successful use of this drug. Similar results with relatively small dosage were recorded by Herrell in a later report,[3] by Florey and Florey,[4] and Dawson and Hobby.[5] The latter authors, however, were successful in the treatment of two cases in which 830,000 units and 1,420,000 units were given over a period of 10 and 33 days respectively. On the other hand, they observed no improvement in two other cases in which 6,670,000 units and 7,960,000 units were administered in 30 and 33 days respectively.

The most encouraging report on penicillin in subacute bacterial endocarditis has come from Loewe and his associates.[6] These workers were successful in arresting the disease in seven of nine patients by employing combined penicillin-heparin therapy. In their opinion heparin "dissolves" vegetations on the heart valves, and permits greater activity of the chemotherapeutic agent. The total dosage of penicillin in their cases varied from 867,920 to 7,890,340 Florey units. The daily dosage varied from 40,000 to 200,000 Florey units and was administered chiefly by the continuous intravenous drip method.

More recently Keefer [7] stated that of 55 cases of bacterial endocarditis reported to the Committee on Chemotherapeutic and Other Agents of the National Research Council, only three were still alive after one year of study. He stated further that several other cases with which he was familiar had received more than 20,000,000 units of penicillin with little or no influence upon the disease.

From these observations it is evident that opinion must be reserved regarding the value of penicillin in subacute bacterial endocarditis until accumulated

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From the Cardiovascular Service, U. S. Marine Hospital.

experience permits an accurate evaluation of this form of therapy. The following case of *Streptococcus viridans* endocarditis appears to have been arrested by this form of treatment.

Case Report

P. P. T., a 21 year old seaman of Italian descent, was admitted to the hospital on December 4, 1943 with the complaint of fever, weakness and generalized aching in the muscles and joints. His symptoms had begun with a "cold" six weeks previously and persisted in varying degree until the time of admission. He received sulfonamide therapy aboard ship for a period of three weeks without clinical improvement. There was a history of an acute attack of rheumatic fever at the age of five with a persistent murmur of the heart dating from that episode. For a number of years he had suffered from chronic sinusitis with recurrent, acute exacerbations.

Examination revealed a slim, well-developed, listless, young male with a characteristic café-au-lait complexion. Temperature was 101° F., pulse 110, respirations 20. The radial pulses were full and bounding, equal and regular. The blood pressure was 125 mm. Hg systolic and 0 mm. diastolic. The apex impulse of the heart was felt in the sixth left intercostal space in the anterior axillary line. There was a systolic murmur of moderate intensity and a mid-diastolic rumble with presystolic accentuation at the mitral area. At the aortic area and along the left sternal border a high-pitched early diastolic murmur was noted. The lungs were clear throughout. The spleen was palpable three fingers'-breadth below the left costal margin. Petechiae were present in the pulps of the fingers and toes and in the left lower palpebral conjunctiva. There was no clubbing of fingers or toes.

Initial Laboratory Data: The blood Wassermann and Kahn reactions were negative. Urine analysis showed normal findings except for a few red blood cells. The blood count revealed 4,500,000 red cells with 14 grams of hemoglobin. There were 11,400 white blood cells per cu. mm. with 74 per cent neutrophiles, 22 per cent lymphocytes and 4 per cent transitionals. The sedimentation rate (Cutler) was 24 mm. per hour.

Electrocardiogram showed normal rhythm with a ventricular rate of 90; bifid P-waves in Leads II and IV; P–R interval .16 sec., QRS interval .08 sec.; tendency to left axis deviation. Bedside roentgen-ray of the chest showed marked enlargement of the cardiac shadow, especially to the left, with prominence of the right auricular border.

Blood culture drawn on December 7 was positive for *Streptococcus viridans*, showing 128 colonies per cubic centimeter of blood.

In vitro tests of the susceptibility of this strain of the organism to sulfonamides showed it to be unaffected even in concentrations up to 30 mg. per cent. Sulfadiazine exhibited the greatest inhibitory effect. In vitro studies also showed this strain to be resistant to relatively high concentrations of penicillin.

Inasmuch as penicillin was not available at the time, intravenous medication with the sodium salt of sulfadiazine was begun on December 15. Eight grams of the drug were given at once followed by one gram every four hours thereafter. The temperature returned to normal and persisted at this level for three days. A sulfadiazine blood level of 14.8 mg. per cent was reached on the third day, but the development of oliguria and hematuria necessitated the discontinuance of the drug.

Penicillin therapy was begun on December 18 in the dosage of 50,000 units intramuscularly every four hours (300,000 units daily). This amount was employed for two days and then for the next three days the dosage given varied between 65,000 units and 75,000 units every four hours. The total number of Florey units administered in the period of five days was 1,840,000. The patient's temperature remained normal throughout this time except for a single elevation which followed a trans-

fusion of 500 c.c. of blood. Immediately upon the discontinuance of penicillin, sulfadiazine was administered in moderate dosage. Blood culture had been sterile the day penicillin was started and remained so throughout its use. The patient seemed to improve clinically. Fresh petechiae, however, were noted in the left lower palpebral conjunctiva and on the left index finger on December 22. The following day two more appeared in the left palm. Sulfadiazine blood levels were maintained at about 7 mg. per cent until December 30 when the drug was discontinued. On January 4 the spleen was no longer palpable, there were no fresh petechiae, and the temperature was still normal. The following day, however, the patient developed an acute pharyngitis; there was an elevation in temperature and blood culture was again positive for *Streptococcus viridans*, showing six colonies per cubic centimeter of blood. Sulfadiazine was started orally, and by means of supplementary intravenous injections of sodium sulfadiazine a blood level of 15 mg. per cent was attained. Signs of sulfonamide toxicity again developed and on January 14 the drug had to be halted despite a positive blood culture. The temperature had remained normal throughout the course of sulfadiazine, but upon its withdrawal fever again developed. The patient complained of malaise, anorexia, generalized joint pains, and swelling and tenderness under the left eye. No new petechiae were noted, however.

On January 19 blood culture was still positive for *Streptococcus viridans* and on that date penicillin therapy was again instituted, this time by the continuous drip method. The drug was administered throughout the day and night. The 24 hour dosage was 360,000 units dissolved in a liter of normal saline. To the solution of penicillin in saline, 80 mg. of liquaemine was added on the first day; subsequent dosage of liquaemine was 60 mg. every 24 hours. Clotting time by the Lee-White method at the commencement of penicillin-liquaemine therapy was seven minutes. The next day the clotting time was still seven minutes and fresh petechiae appeared in the left lower palpebral conjunctiva. The patient remained quite sick and the temperature varied between 102° F. and 104° F. for the next few days in spite of negative blood cultures. On January 22 dosage of penicillin was increased to 500,000 units per day but the temperature persisted in its elevation. The patient felt cold, sweated profusely and suffered several severe chills. Clotting time remained unchanged. On the afternoon of January 24 the temperature began to climb and reached a peak of 107° F. in the early evening. The heart rate at this time was 190 per minute and the patient appeared extremely ill. He was packed with iced towels for two hours with a fall in temperature to 103.6° F. A fresh solution of penicillin and liquaemine was made up and administered in a carefully sterilized infusion set in an attempt to eliminate possible pyrogenic factors. The temperature, however, rose again to 106° F. during the night and remained at that level until the following morning when the infusion was stopped. With discontinuance of the intravenous penicillin and liquaemine, the temperature immediately dropped to 96° F. and then rose to normal. Penicillin was then administered by intramuscular injection in the dosage of 75,000 units every three hours (600,000 units daily). On January 27 the daily dosage was reduced to 500,000 units per day (62,500 units every three hours), and on this schedule the patient continued to show progressive clinical improvement. His course remained afebrile, and repeated blood cultures were negative. The drug was discontinued on February 3. The only supplementary medication during the penicillin therapy was a blood transfusion. The total dosage of penicillin during the second course of administration was 7,519,000 units over a period of 16 days. Thirteen hours before the last dose of penicillin was given, the administration of sulfadiazine was begun. The blood level was first built up by intravenous injection of the sodium salt and then maintenance dosage was started orally. A level of 5–7 mg. per cent was maintained for a period of three weeks and then the drug was discontinued.

In an effort to combat the chronic sinus infection a nebulizer containing penicillin solution was employed. Patient, when last examined, had gained considerable weight

and appeared robust. Temperature and pulse rate had remained normal and the blood stream was sterile. Blood picture, urinalysis and sedimentation rate were within normal limits. Subjective and objective improvement had persisted without remission for a period of six months.

Discussion

The introduction of penicillin again raises the hope that an effective therapeutic agent for subacute bacterial endocarditis may be at hand. Reports in the literature to date, however, offer a confused picture and although numerous failures have been recorded it must be admitted that dosage, method of administration, and duration of therapy have not been satisfactory in many instances. From purely theoretical considerations it would seem that effective therapy demands not only (1) an adequate penicillin blood level to sterilize the blood stream but also (2) a maintenance of this level for sufficient time to permit sterilization and organization of the vegetations on the heart valve. In the case herein reported we were unsuccessful in our first attempt to attain these objectives. Thus it was found that the four-hourly injection of penicillin resulted in an effective blood level only for one and one-half to two hours after each injection. Thereafter, the concentration of the drug fell below the level necessary to inhibit growth of the organism as determined by previous in vitro studies. Inasmuch as the duration of treatment was only five days, we attempted to supplement this therapy with sulfadiazine when the supply of penicillin was exhausted. The return of a positive blood culture several days after all therapy was discontinued testifies to the inadequacy of this form of management.

In view of these considerations, the second course of penicillin was initiated by the continuous intravenous drip method in an attempt to maintain a constant, effective blood level of this drug. It must be emphasized that heparin was used solely for the purpose of preventing clot formation within the needle and not to increase the coagulation time of the blood as recommended by others.[6] The continuous drip method was employed for five days, at the end of which time sensitization to heparin as manifested by hyperpyrexia necessitated its withdrawal. Penicillin was then administered intramuscularly every three hours in appreciably larger dosage. Blood studies indicated that an adequate level of penicillin was reached and maintained throughout this apparently successful course of therapy.

Summary

A case is presented in which 7,519,000 Florey units of penicillin, administered over a period of 16 days, were effective in arresting a case of subacute bacterial endocarditis which had not responded to massive sulfadiazine therapy. No clinical or laboratory evidence of bacterial activity has been present for the past six months.

Addendum: Physical examination in February 1945, twelve months after discontinuance of penicillin therapy, revealed no evidence of infection. Blood culture was negative.

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SUBACUTE BACTERIAL ENDOCARDITIS COMPLICATED BY AGRANULOCYTOSIS; REPORT OF CASE WITH RECOVERY *

By Henry I. Russek, M.D., Richard H. Smith, M.D., *Staten Island, New York,* and Burton L. Zohman, M.D., F.A.C.P., *Brooklyn, New York*

The superiority of penicillin over all other agents thus far employed in the treatment of subacute bacterial endocarditis appears to be established.[1, 2, 3, 4, 5, 6] That penicillin may similarly prove to be an important advance in the therapy of agranulocytosis has been hypothesized on the basis of the low toxicity of the drug combined with its high antibacterial potency.[7] Supporting this view is the record of three successfully treated cases already reported in the literature.[8, 9]

The occurrence of agranulocytosis in a case of *Streptococcus viridans* endocarditis provided an opportunity for testing the effectiveness of penicillin in both conditions simultaneously. The purpose of this paper is to record the first case of recovery from this combination of diseases.

Case Report

F. M., a 21 year old white merchant seaman, was admitted to the U. S. Marine Hospital on May 29, 1944 complaining of fever and joint pains of four weeks' duration. Past history was negative except for an attack of rheumatic fever in 1936.

Physical examination revealed a typical café-au-lait complexion. Temperature was 101° F. The mucous membranes were pale. Petechiae were noted in both lower palpebral conjunctivae. Examination of the heart revealed a high-pitched diastolic murmur in the third left intercostal space close to the sternum. There was a loud systolic murmur at the mitral area. This murmur was transmitted to the axilla. The blood pressure was 120 mm. Hg systolic and 40 mm. diastolic. The spleen was palpable two fingers'-breadth below the left costal margin.

Roentgen-ray examination revealed a mitral configuration of the heart.

Laboratory studies showed a positive blood culture for *Streptococcus viridans* on June 11, 13, 20 and 30 and on July 11, 17 and 24. Blood count on admission revealed

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3,020,000 red blood cells with 50 per cent hemoglobin. There were 12,050 white blood cells with a differential count of 66 per cent neutrophiles, 26 per cent lymphocytes, 7 per cent transitionals and 1 per cent eosinophiles. Urinalysis showed a moderate amount of albumin and many red blood cells. Sedimentation rate by the Wintrobe method was 28 mm. in one hour. Wassermann and Kahn serologic reactions were negative.

On July 11, the patient was given sulfadiazine, 4 grams immediately, and 1 gram every four hours for 14 days. There was no clinical improvement as shown by the accompanying chart (chart 1). Fresh petechiae were noted and the blood culture

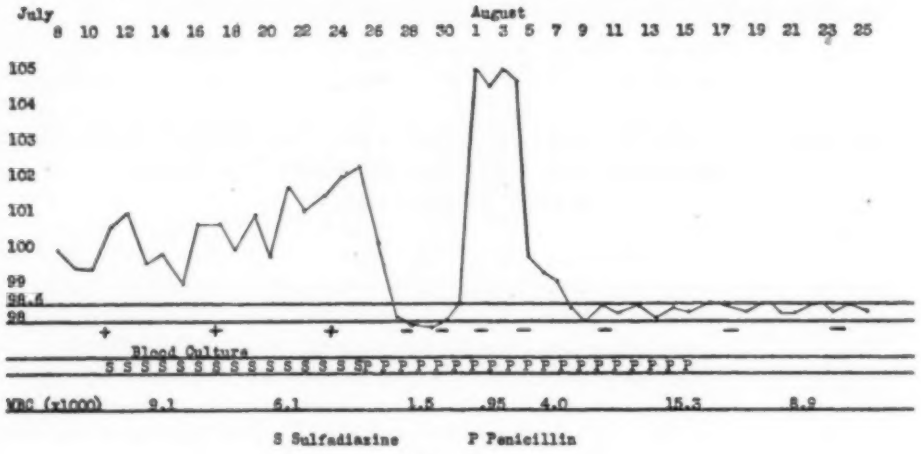

CHART 1.

remained positive for *Streptococcus viridans*. A blood count on July 21 revealed 6,100 white blood cells, of which 66 per cent were neutrophiles. An erythematous, macular rash appeared over the trunk and limbs and was attributed to drug therapy. On July 25, sulfadiazine was discontinued and a course of penicillin was started in the dosage of 50,000 units every three hours. The temperature returned to normal within 24 hours and there was distinct clinical improvement. Repeated blood cultures were negative. On July 29, four days after sulfadiazine was discontinued, a blood count showed 1,500 white blood cells with 54 per cent neutrophiles, 43 per cent lymphocytes and 3 per cent monocytes. The red cell count and hemoglobin were essentially unchanged. Patient gave no history of previous sulfonamide therapy.

On August 1, the temperature rose to 105° F. The throat was mildly congested but there was no lymphadenopathy. The blood picture showed 2000 white blood cells with 89 per cent lymphocytes and 11 per cent monocytes. No granulocytes could be found in the blood smear. Blood culture remained negative. On August 2 there were 950 white blood cells, none of which belonged to the granulocytic series. Beginning on August 3, pentnucleotide (10 c.c.) and liver extract (15 U.S.P. units) were given intramuscularly once each day. Penicillin therapy was continued as before. A transfusion of 500 c.c. of whole blood was given on August 3 and repeated on the following day. On August 5 there were still no granulocytes in the blood smear. On August 7 the white cell count rose to 4000; the differential count showed 43 per cent neutrophiles, of which 23 per cent were band forms. Myelocytes and metamyelocytes also made their appearance (table 1). Congestion of the pharynx subsided and the temperature dropped to normal and remained at this level. Subsequent blood studies showed a normal total and differential count. On August 12 the administra-

TABLE I

Blood Studies

Date	W.B.C.	Neutrophiles		Remarks
		Polys	Bands	
6–11–44	8,550	70%	—	—
7–11–44	—	—	—	Sulfadiazine started
7–14–44	9,100	68%	8%	—
7–21–44	6,100	54%	12%	—
7–25–44	—	—	—	Sulfadiazine discontinued Penicillin started
7–29–44	1,500	54%	—	—
8– 1–44	2,000	No granulocytes		Lymphocytes 89% Monocytes 11%
8– 2–44	950	No granulocytes		—
8– 3–44	—	—	—	Pentnucleotide and liver extract started
8– 5–44	1,450	No granulocytes		—
8– 7–44	4,000	20%	23%	Metamyelocytes 6% Myelocytes 3%
8– 9–44	8,850	34%	22%	Myelocytes 2% Premyelocytes 2%
8–12–44	18,150	39%	14%	Premyelocytes 4%
8–12–44	—	—	—	Pentnucleotide and liver extract discontinued
8–15–44	15,300	54%	12%	Penicillin discontinued
8–22–44	8,950	50%	1%	—
10– 6–44	7,650	58%	2%	—

tion of pentnucleotide and liver extract was terminated. On August 15 penicillin was similarly discontinued, the total dosage having been 8,400,000 units over a period of 21 days. The patient has remained clinically well without further treatment. Blood cultures have been persistently negative and the blood picture has remained normal to date.

SUMMARY

A case of subacute bacterial endocarditis is reported in which agranulocytosis developed as a complication of sulfadiazine therapy. Recovery from both diseases resulted from the administration of 8,400,000 units of penicillin over a period of 21 days.

Addendum: Examination 8 months after discontinuance of penicillin therapy revealed no clinical or laboratory evidence of bacterial activity.

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GUMMATOUS AORTIC VALVULITIS: REPORT OF CASE *

By S. H. AUERBACH, M.D., *Augusta, Georgia*

CHRONIC aortitis is the most common tertiary lesion of acquired syphilis and deformity of the valve with incompetence is a customary sequel. The characteristic aortic lesion is essentially an endarteritis,[1] followed by necrosis and sclerosis of the media. The adjacent vascularized portions of the valve cusps are affected in the same manner.[2] The destructive process rarely approaches the formation of gummas other than microscopic. Thus, Gordon, Parker and Weiss [3] were able to collect only seven adequately described cases of frank gummatous aortitis in the literature to 1942 in a report of three additional cases.

Gummatous destruction of the aortic valve is also rare. Nineteen acceptable cases of gummatous cardiac valvulitis were collected by Sohval [4] in 1935 and he added another. Of these 20 cases, eight involved the aortic valve. Five of these were without microscopic confirmation of the syphilitic nature of the disease. In four the valvular lesions resulted from spread of gummatous processes primarily involving other cardiac structures. Richter [5] reported the ninth case of gummatous aortic valvulitis in 1936 and successfully demonstrated treponemata in the diseased cusps.

We present an additional case of gummatous aortic valvulitis, the second report in which the causative organisms were demonstrated.

CASE REPORT

K. G., a 65 year old Negro male, was admitted to the University Hospital on December 20, 1942, complaining of shortness of breath. He dated the onset of his illness to a time about seven months before admission, when he began to experience some dyspnea on exertion and occasional attacks of swelling of the feet and ankles after standing for long periods. He was able to continue working until one month before admission when exaggeration of the symptoms necessitated rest. Dyspnea now occurred without exertion and seemed worse at night. A physician was called who gave him "drops" for a "weak heart." He felt somewhat improved from the medication but was never entirely relieved. He gave no history of precordial pain or hemoptysis.

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From the Department of Pathology, School of Medicine, University of Georgia, Augusta, Georgia.

The record showed four previous admissions to the hospital. The first, in 1929, was for a foreign body in the pharynx and is important in the present study only in the incidental finding of a positive blood Wassermann reaction. In the following years he reported to the outpatient department at irregular intervals for antisyphilitic treatment. In 1930, there were admissions for periurethral abscess and urethral fistula, and in 1934 an admission for a gunshot wound of the right eye for which the globe was enucleated.

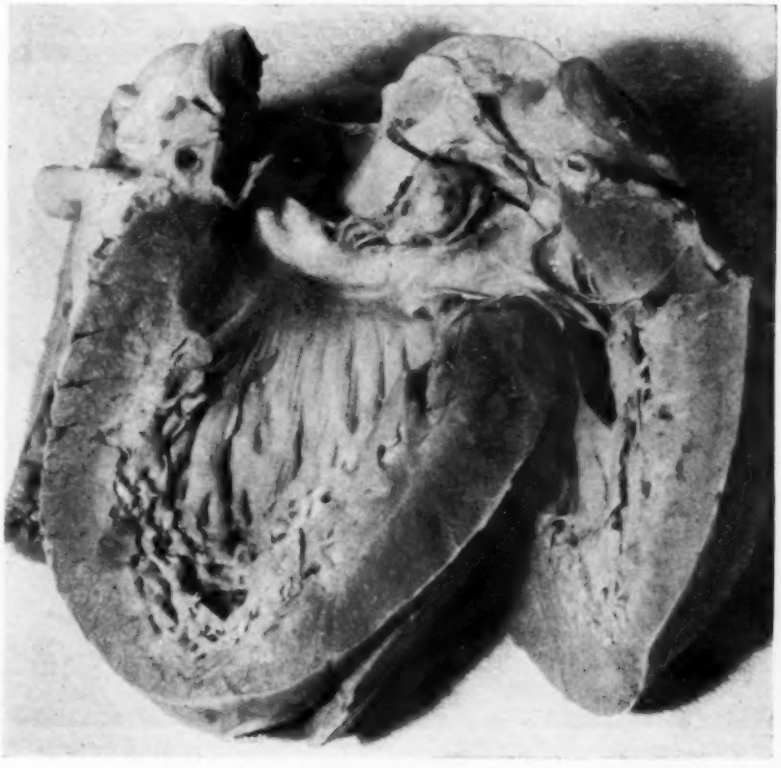

FIG. 1. General topography of the left ventricle and aortic valve.

The past medical history included a vague story of "rheumatism" at 15 years of age, with subsequent irregular recurrences during the spring months. There was a questionable episode of swelling of the ankles at the age of 30. He gave a history of gonorrhea 25 years before his last admission and of a penile sore about 15 years before.

The family history was irrelevant. Both parents died in old age. A long list of siblings was dead but the causes were unknown to the patient. He denied a family history of heart disease or arthritis.

Physical Examination: He was fairly well developed and nourished. There was moderate respiratory distress, but he was able to lie flat. Respirations were rapid and somewhat labored. The percussion note over the chest was resonant, but there were moist râles over both lung fields. The heart was not enlarged. There was a distinct thrill over the precordium and the heart sounds were all but replaced by a loud, low-pitched, to-and-fro murmur which was most pronounced in the mitral area. The pulse rate was 92 and the rhythm was regular. Blood pressure was 138 mm. Hg

systolic and 90 mm. diastolic. There was irregular scarring of the glans and prepuce with multiple fistulas and false passages. There was slight pitting edema of the ankles.

Laboratory Data: The red corpuscles numbered 4.20 million and the hemoglobin measured 11.5 gm. The leukocyte count was 8,000 with 62 per cent polymorphonuclears. The urine on admission showed 2+ albumin and numerous leukocytes in the sediment. The blood non-protein nitrogen was 39 mg. Blood Wassermann and Kahn tests were positive. A roentgen-ray plate of the chest showed no cardiac enlargement. An electrocardiogram seven days after admission showed only digitalis effect.

FIG. 2. Detail of aortic valve. The slip of black paper extends through one of the large fenestrations.

The clinical diagnosis was: Heart disease, probably rheumatic, with mitral insufficiency and stenosis. Two observers mentioned aortic stenosis and regurgitation as possibilities. Under appropriate treatment there was some symptomatic improvement. The respiratory embarrassment was relieved and the urine became normal. The temperature remained flat throughout the period of hospitalization. He complained of some pain on the twenty-first hospital day and died quietly during the afternoon. There was no notable change in physical findings during this period.

Necropsy: The examination was performed 21 hours post mortem.

The pericardial sac was normal and the epicardium was smooth and glistening. The heart weighed 395 gm., a moderate relative enlargement. Both ventricles were slightly dilated with fluid blood and postmortem clots. The myocardium was soft. The mural endocardium of the left ventricle was slightly thickened. The mitral, tricuspid and pulmonic valves were well preserved and all were competent; these measured 9, 14 and 8 cm. respectively. The aortic ring measured 7.5 cm. There was

some general sagging of the cusps so that the coronary orifices were at the level of the free margins (figure 1). Aside from slight fibrous thickening, the left cusp showed nothing unusual. The commissural attachment between the right and posterior cusps was disrupted, converting these sinuses into a single chamber (figure 2). That portion of the common leaflet representing the posterior cusp was transformed into a flat thickened yellowish mass measuring 2.2 cm. transversely, 1.3 cm. perpendicularly and 0.2 to 0.3 cm. in thickness. The surface was rather irregular and was covered in part with a thin coat of blood and fibrin. It was largely detached from the aortic ring by two fenestrations at the base, the larger of these

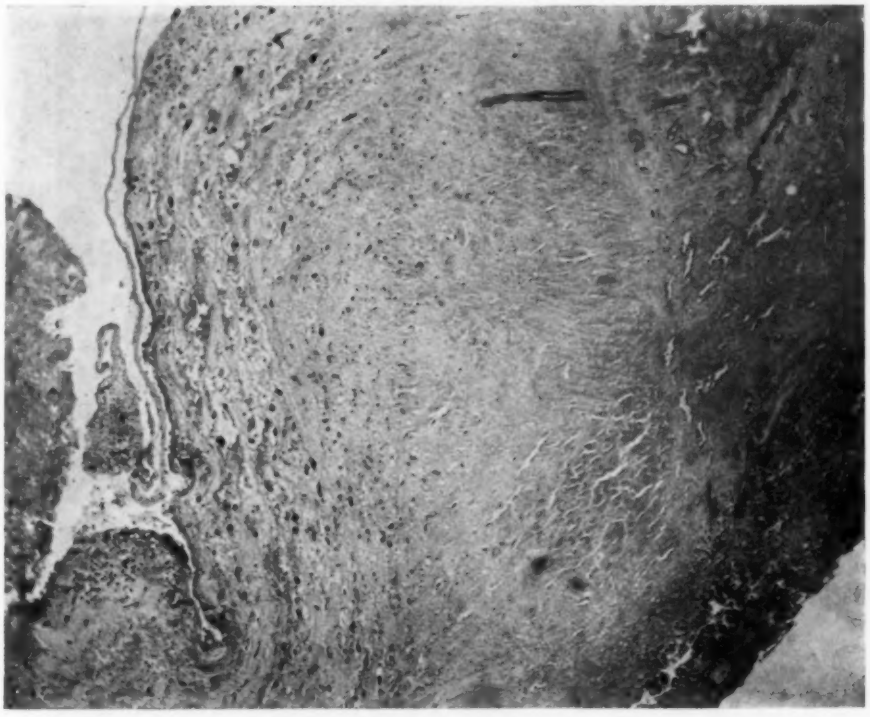

FIG. 3. Photomicrograph of the aortic lesion showing central necrosis and peripheral cellular response. Treponemata were numerous in this necrotic area. × 200.

windows being 1.5 cm. in length (figure 2). Two persistent membranous strips served to connect the remains of the cusp to the ring and to the right cusp. The latter showed a small fenestration at the commissural junction. There was a small yellowish nodulation on the aortic wall at the junction of the left and posterior cusps.

The arch of the aorta was remarkably free from gross evidence of disease. There was moderate atherosclerosis of the distal portion. Both coronaries showed some sclerosis but both were patent; the orifices were wide.

Microscopically, the distal portion of the posterior cusp represented by the yellowish mass showed widespread coagulation necrosis surrounded by a mantle of fibroblasts and numbers of infiltrating plasma cells, macrophages, lymphocytes and polymorphonuclear leukocytes; occasional multinucleated giant cells were present (figure 3). In some areas the necrosis presented a more caseous character and polymorphonuclears were more abundant. There was active fibrosis approaching the

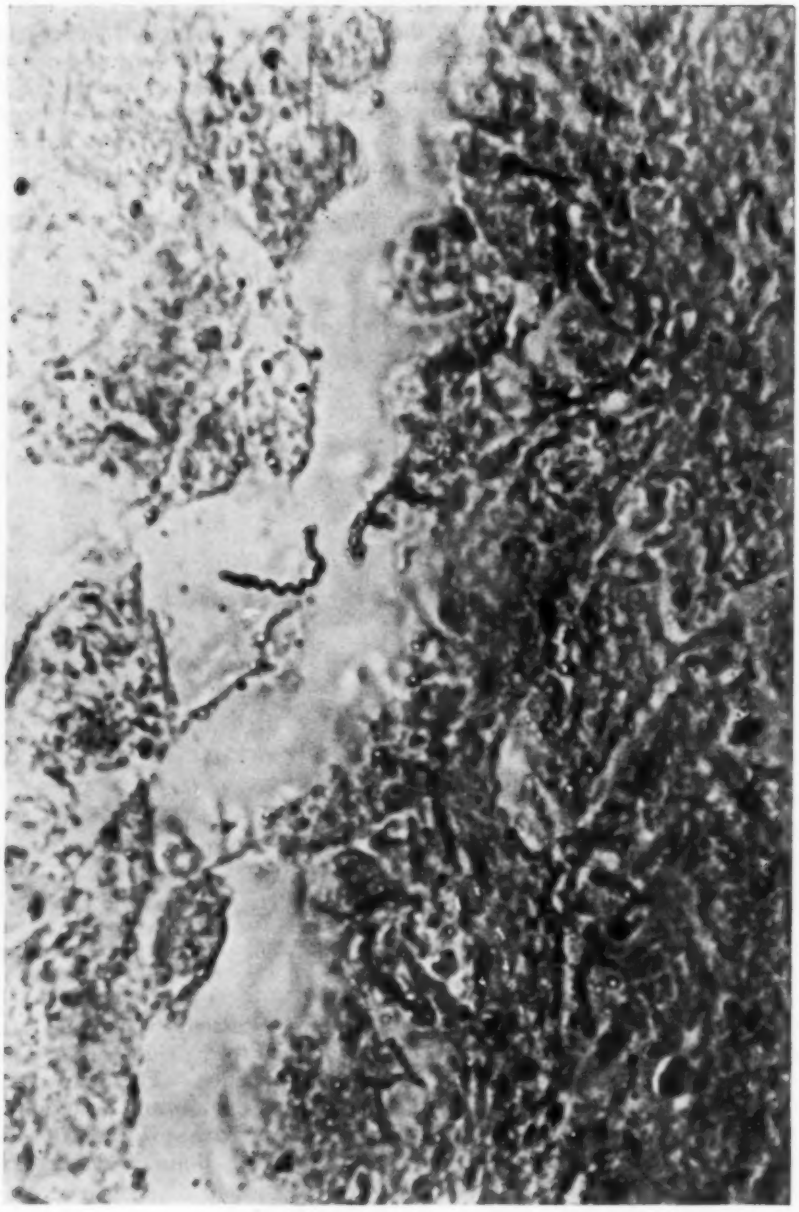

FIG. 4. The organisms as seen in silver preparations. Only a single spirochete is in clear focus. × 1290.

base of the valve and leukocytes were fewer in number. At the line of attachment were several entering blood vessels, each surrounded by plasma cells and lymphocytes. The annulus was comparatively unaffected. In the proximal termination of the media of the aorta, however, there was a fairly diffuse infiltration of leukocytes and occasional minute areas of necrosis were present. In a section of the aorta distally, though within the pericardium, there was microscopic evidence of syphilis. The adventitia was fibrotic and the vasa vasorum showed endarteritis with perivascular round cell infiltration. The outer third of the media was involved. Numerous treponemata were demonstrable in the necrotic portion of the valve in silver preparations stained by the Dieterle method [7] (figure 4). None was found in the fibrous portion of the valve nor in the adjacent aorta.

The myocardium showed some hypertrophy of the fibers. No Aschoff bodies were found. The endocardial fibrous thickening of the left ventricle was patchy in distribution and appeared to be of vascular origin. Other lesions of significance in the case were: passive congestion of the lungs; purulent bronchitis; chronic pyelonephritis of the right kidney; agenesis of the left kidney; chronic cystitis; chronic prostatitis and early adenocarcinoma of the prostate.

Comment

We agree with Sohval [4] that "acquired syphilis has not yet been proved to originate in a valve." In all the reported cases of valvulitis, including the present study, evidence of prior or at least concurrent syphilis of an adjacent structure is present, and it is reasonable to assume that the more natural site first bears the brunt of disease. Those cases of aortic valvulitis which are fully described were preceded by aortitis (with aneurysm in three) or interventricular septal gumma, and the cusps were involved by simple extension. The case described by Richter [5] and this study have one feature in common which is unusual, namely, an acuteness of the valvular lesion to the extent of overshadowing the underlying aortitis. It is of interest that a disease which characteristically attacks the aorta in a chronic manner and involves the valve only secondarily does rarely reverse its natural history and destroy the valve in a stage when the aortic lesions are comparatively insignificant.

Several possible attenuating factors have been brought out previously but we cannot reconcile this case with the suggestions. Gordon, Parker and Weiss have pointed out the relatively high incidence of combined rheumatic heart disease and gummatous aortitis and raise the question "as to whether rheumatic fever, which is prone to produce an acute cellular hyperergic reaction in the myocardium or in the root of the aorta, enhances the tendency toward the development of gummas, particularly in patients who have received but partial antisyphilitic treatment." Only the latter factor could pertain to this case, despite the presumptive clinical diagnosis of rheumatic carditis; the absence of gross or microscopic evidence of the disease is virtually exclusive. Insufficient and sporadic antisyphilitic treatment is an undeniable possibility as a factor but such self-mistreatment has been common among those of the patient's social stratum whereas cardiac gummata have remained extremely rare. Norris [8] and others have mentioned youth as an element which might influence the course of events. This patient was 65 years old, and was known to have had syphilis for 13 years and had probably been infected for at least 15 years. Nor was there a preëxisting valvular defect as in Richter's case (congenitally bicuspid valve

and subaortic stenosis) which could conceivably influence the development of such a lesion.

Clinically, gummatous valvulitis is of little practical importance because of its rarity. The diagnosis has not been established ante mortem and no signs of sufficient constancy to suggest the diagnosis have been noted. The signs and symptoms, as well as other data, vary with the location and nature of the "primary" lesion. It does, however, constitute a possibility to be borne in mind with puzzling cardiac disease occurring in syphilitics.

Summary

The twenty-second case of gummatous valvulitis is reported, the tenth case involving the aortic valve, and the second in which the causative organisms were successfully demonstrated.

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FULMINATING PURPURIC MENINGOCOCCEMIA (WATERHOUSE–FRIDERICHSEN SYNDROME) WITH RECOVERY *

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Recoveries in cases of fulminating purpura of infectious origin, the so-called Waterhouse-Friderichsen syndrome,[1] are extremely infrequent. Of 130 cases of the disease collected from the literature to October 1943, we have been able to find but five cases not ending fatally.[2, 3, 4, 5, 6] We should like to add a sixth case of recovery.

* Received for publication January 15, 1944.
From the Department of Medicine of the Beth-El Hospital, Brooklyn, N. Y.

Case Report

G. R., an adult white female, the hospital bacteriologist for 15 years, was admitted to the Beth-El Hospital late on the morning of March 4, 1943. On the preceding day she had, late in the afternoon, complained of being somewhat tired but at that time showed no pyrexia, and superficial physical examination was negative; in particular there was no purpura nor cyanosis. She left the hospital at 7 p.m. that day planning to attend a scientific meeting that night. Two hours later she suddenly experienced a series of chills, each of a few minutes' duration, the entire series lasting over a period of about half an hour. Rectal temperature taken at that time was 101° F. Examination by an ambulance surgeon was entirely negative save for an intense congestion of the pharynx, marked cyanosis of the lips, and a moderate diffuse duskiness of the body; no purpura was present, pulse was not rapid and of good quality. Grippe was suspected and hospitalization advised, but this was refused because of the severe snowstorm then raging. The remainder of the night was spent in sleeplessness in spite of marked drowsiness, frequent severe chills, and an intermittent but increasingly more marked sense of abdominal fullness and pressure, relieved at first for short intervals by dribbling urination. Toward morning the abdominal pain had become very severe and cramp-like. She was totally unable to void. She remained conscious and rational throughout this period, issuing instructions as to some of her possessions just prior to her removal, by ambulance, to the hospital at 11 a.m. She even insisted on dressing herself and walking, with but slight assistance, to the vehicle.

Her health prior to the present episode had always been good save for a long-standing localized skin induration of both mid-anterior tibial regions, diagnosed by biopsy as atypical scleroderma. This condition had shown no progression for the last five years. During the last seven years she had shown occasional red cells and a very rare hyaline cast in centrifuged urinary specimens, and had constantly maintained a blood urea nitrogen level in the vicinity of 21 mg. per c.c. Several urea clearance tests showed 75 to 85 per cent standard clearance. Blood pressure was never higher than 150 mm. Hg systolic and 74 mm. diastolic. Her skin capillary resistance was apparently considerably reduced, the tourniquet (Rumpel-Leede-Hess) test showing never less than 50 and on several occasions as many as 200 petechial spots. The last such test was performed about two years prior to the present illness and showed 100 petechiae. Extensive investigations failed to reveal any allergic factors; numerous hematologic studies failed to show any evidence of blood dyscrasia; her diet was not deficient in vitamin C, and the administration of large added amounts of vitamin C and of vitamin P did not apparently affect the results obtained on tourniquet test, nor the microscopic urinary findings. She did not bruise easily. No focal infection was ever found. It was believed that she had a fragile capillary system of unknown etiology, that this probably accounted for the urinary findings, that there was no apparent progression of the process, that it was probably clinically of no significance, and that no treatment was necessary. Throughout this entire period she had been carrying on her extensive routine and research work without difficulty.[7]

Admitted to the hospital some 10 minutes after leaving her home, she was still conscious, but lapsed suddenly into coma while talking to the interne who had just obtained a fragmentary statement as to her present illness. Temperature at this time was 105.4° F., pulse 110, very feeble, easily compressible, and with frequent extrasystoles, respiratory rate 30. Blood pressure was 90 mm. Hg systolic and 60 mm. diastolic. There was no nuchal rigidity; all reflexes were somewhat sluggish but equal, and there were no pathologic reflexes. A massive purpuric rash was diffusely scattered over her abdomen, and to a lesser extent, her chest and back; on her arms and legs, particularly around the wrists and ankles, a similar coarse and fine purpuric rash was present. The hemorrhages ranged from bright red to purple, were entirely macular and serpiginous, were not ulcerated, and were sharply defined though fre-

quently confluent or grouped. Both the ecchymoses and the petechiae showed an underlying and surrounding bluish or purplish tint not disappearing on pressure. On the hard palate four similar blue-red hemorrhages were present. The lips were cyanosed deeply, the remainder of the body of an ashen hue. The body was hot, the extremities cold. Heart sounds were rapid, distant, and very feeble. Lungs were clear, respirations shallow. Abdomen was slightly distended, soft, and tympanitic; no viscera were palpable, the splenic dullness was not increased. Catheterized urine showed a faint trace of albumin, an occasional red cell and hyaline cast. Blood count showed 3,700,000 red cells, 11.5 gm. hemoglobin, 250,000 platelets, 17,000 white cells of which 1 per cent were myelocytes, 47 per cent metamyelocytes, 11 per cent staff neutrophiles, 25 per cent segmented neutrophiles, 12 per cent lymphocytes, 1 per cent Turck cells, and 3 per cent monocytes; no toxic granules were present.

Five cubic centimeters of digifoline and an equal amount of caffeine sodium benzoate were immediately administered hypodermically; 4 ounces of coffee and 2 grams of sulfadiazine were given by gavage. One hour thereafter 5 grams of sodium sulfadiazine in 100 c.c. normal saline were administered intravenously. Her blood pressure meanwhile had fallen to 60 mm. Hg systolic and 50 mm. diastolic, despite further digifoline-caffeine and coramine therapy, and one hour after the intravenous injection had been completed both the blood pressure and the peripheral pulse were unobtainable. At this time, the coma was most profound and very slight resistance of the neck was present. Her back and buttocks had taken on a pronouncedly mottled appearance resembling postmortem lividity and similar areas were noted on the posterior thighs, ankles, and over the deltoid regions.

At 5 p.m., six hours after admission, 10 c.c. of adrenal cortical extract (Upjohn) and 1,000 c.c. of 10 per cent saline containing 5 grams of sodium sulfadiazine were administered intravenously at the rate of 30 drops per minute. Seven hours later 1,000 c.c. of 5 per cent glucose in normal saline containing 10 c.c. of adrenal cortical extract were similarly administered. One gram of sulfadiazine was given by gavage every four hours. On the morning after admission, the temperature had fallen to 99.8° F., the pulse was 108, regular and of fair quality, and the blood pressure was 70 mm. Hg systolic and 50 mm. diastolic. That afternoon the temperature had further fallen to 98° F.; thereafter it slowly rose to between 100° and 101° F. for the six days during which oral sulfadiazine was continued, receding to 98.6° F. as soon as the drug was discontinued.

By morning of her second day in the hospital the patient was again conscious and rational, thereafter slowly recovering from a very profound weakness and an asthenia so severe that attempting to stand was difficult three weeks after admission. The adrenal cortical extract, 10 c.c. daily in two divided doses intramuscularly, was continued for four days; she received in all 60 c.c. of the extract, a third of this during the first 18 hours of her stay. On the afternoon of her second day in the hospital (by which time she had received 20 c.c. of adrenal cortical extract and 180 grams of sodium chloride intravenously) the blood pressure was 92 mm. Hg systolic and 70 mm. diastolic. On the third day, and thereafter until the twelfth day, the blood pressure was 120 mm. Hg systolic and 70 mm. diastolic; on the twelfth day it was 146 mm. systolic and 80 mm. diastolic; on the thirteenth day and thereafter until discharge on the twentieth day, it was 150 mm. systolic and 80 mm. diastolic. Two months after her discharge, and again on numerous occasions thereafter until this report, nine months after discharge, it remained at the level last noted in the hospital.

Oral sulfadiazine, 1 gram every six hours, was continued until the seventh day of her hospital stay; in all, she received 39 grams of the drug, 15 grams of this in the first 24 hours, 10 grams of which were given intravenously. Red cells and occasional granular and hyaline casts were noted in all urinary specimens from the third to the twelfth day. Acetylsulfadiazine crystals were noted only on the fourth and

fifth days. Urinary output and analyses, and blood chemical determinations are noted in table 1.

The purpuric rash began to fade from the body and extremities within the first 24 hours, had completely disappeared by the fourth day, and left no residual skin changes. The oral hemorrhages ulcerated on the eighth day, but had completely healed, upon the application of gentian violet locally, by the twelfth day. On the

TABLE I

Urinary and Blood Chemical Findings, Case of Waterhouse-Friderichsen Syndrome

Date	Fluid Intake	Urine				Blood					
		Output	Sp.Gr.	Alb.	Casts	Sulfadiazine (mg. %)	Urea (mg. %)	Total Protein (gm.)	A.G. ratio	Sodium (meq. L)	Chloride (mg. %)
3/4	1700	450	1018	2+	hyaline 4+						
3/5	2140	1480	1012	3+	hyaline 1+	25.3	49.5	6.28			
3/6	2580	1090	1020	4+	hyaline 4+	17.0	37.5				
3/7	1380	840	1022			5.6	22.2				
3/8	1530	1140	1012	3+	hyaline 4+						
3/9	1500	1920	1010	2+	granular 1+						
3/10	1210	3750	1006	0	0						
3/11	1950	1680	1012								
3/12	1980	1240	1012								
3/13	1710	1500	1018								
3/14	1260	1400	1014								
3/15	1410	1950	1010	0	0						
3/16	1200	1860	1010	2+	granular 1+		34.0	5.2	2.1:3.1		
3/17	1200	1280	1010	2+	0						
3/18	1680	980	1020								
3/19	790	990	1018	ft.	granular 1+						
3/26			1018	0	0		21.0	6.2	3.4:2.8		
5/25			1016	0	0		21.4	6.8	4.8:2.0	136	512

seventh day a crop of herpetiform vesicles appeared on the neck just below and to the right of the mandibular symphysis; these slowly dried and were gone by the seventeenth day.

A blood culture taken on admission showed a heavy growth of *Neisseria intracellularis* (meningococcus) type 1 on the second day. Subsequent blood cultures were sterile. Direct smears from the hemorrhagic skin lesions showed intracellular Gram-negative diplococci. Spinal tap was never performed since, with the exception of the transient nuchal rigidity appearing on the day of admission and disappearing within five hours, no neurological signs were ever noted.

Diffuse pitting edema of the legs and thigh was noted on the twelfth day and coincided roughly with a rise in blood urea nitrogen, diminution in total protein, and slight inversion in the A : G ratio. The protein content of her diet was increased to 200 grams, and the edema slowly disappeared, was completely absent by the twentieth day. At this time the blood urea nitrogen level was normal, the blood protein level elevated to 6.2 grams, the A : G ratio 3.4 : 2.8. Two months after discharge, the blood protein level was 6.8 grams, the A : G ratio 4.8 : 2 (table 1). No further edema was noted.

No blood sodium or chloride determinations were performed while the patient was in the hospital. Two months after discharge, the blood sodium was 136 meq./L, the blood chlorides 512 mg. per cent. These determinations were performed at this time, and will be repeated periodically, in an attempt to evaluate whether the adrenal glands have suffered any permanent damage. Hematologic studies performed during the acute illness and two months after leaving the hospital are summarized in table 2.

TABLE II

Hemograms in Case of Waterhouse-Friderichsen Syndrome

Date	RBC (million)	Hgb. (grams)	Platelets	WBC	Myelocytes (%)	Metamyelocytes (%)	Staff cells (%)	Segmented cells (%)	Eosinophiles (%)	Lymphocytes (%)	Monocytes (%)	Turck cells (%)	Toxic Granules (% WBC)
3/4	3.7	11.5	250,000	17,000	1	47	11	25		12	3	1	none
3/6	3.7	11.5	250,000	24,000	4	52	11	29		3	1		100%
3/8	3.4	10.5	260,000	13,000	3	35	10	22	3	24	3		80%
3/10	3.5	10.5	270,000	13,500	0	15	15	40	3	23	4		70%
3/16	3.7	11.0	270,000	9,600	0	0	5	60	0	27	8		20%*
3/24	3.6	11.0	270,000	6,600	0	0	3	61	1	30	5		none
5/25	3.9	12.4	290,000	6,800	0	0	0	74	1	21	4		none

* All the staff cells and some segmented cells showed toxic granules.

Upon discharge from the hospital on the twenty-first day after admission, there were no residual evidences of the infection nor, with the exception of considerable asthenia, any suggestion of adrenal involvement. No neurologic or mental changes were present—the patient had, in fact, been advising her assistants in the laboratory technically for a week prior to her discharge, had been examining cultures grossly while in bed—and careful examination of the cardiovascular and urinary systems failed to show any evidence of functional impairment. Two months after her discharge she was back at both her routine and experimental work in the laboratory, the asthenia having totally disappeared.

COMMENT

As has frequently been pointed out, a positive diagnosis of adrenal hemorrhage can be made only at autopsy. So uniformly characteristic, however, are the clinical signs and symptoms of fulminating purpura with adrenal hemorrhage, the so-called Waterhouse-Friderichsen syndrome, that a presumptive diagnosis is warranted clinically. If suspected and vigorously treated, dramatic recovery may be achieved in this condition in which until Carey's report [2] in 1940, a fatal outcome appears to have been invariable.

It is not the purpose of this paper to discuss in detail the pathology of the syndrome. Parenthetically it may be noted that the vast majority of proved cases of Waterhouse-Friderichsen syndrome showed extensive hemorrhagic infiltration and massive disorganization of the adrenal glands. Even in those cases showing at autopsy relatively insignificant adrenal hemorrhages, as in the cases of Gordon and Shimkin [8] and of McLean and Caffey,[9] there appears to have been considerable cortical cellular necrobiosis. This necrobiosis, to which little attention appears to have been devoted in the English literature, was strikingly seen by one of us (M. J.) in a fatal case of the disease showing no significant adrenal hemorrhages. To a lesser degree, these can be seen in the adrenal glands of any severe septicemic state in which a clinical picture of circulatory collapse supervenes. It consists of cellular swelling, the total or almost total depletion of cortical lipoids, and varying degrees of cortical nuclear rhexis. In any event, review of the autopsied cases of Waterhouse-Friderichsen syndrome, with or without adrenal hemorrhage, yields morphologic evidence of adrenal insufficiency. According to Herbut and Manges [10] most authors agree that it is the adrenal insufficiency rather than the toxicity that is responsible for the fatal outcome.

The indications for chemotherapy directed toward the infectious agent, which is usually the meningococcus,[10] although various other microörganisms have been reported as etiologic agents, are usually self-evident. Such chemotherapy needs no discussion at this point except to emphasize that it should be vigorous. Of equal importance is therapy directed at tiding over the apparently functionless adrenal glands. This phase will be discussed in detail.

As pointed out by Carey,[2] adrenalin plays no part in the treatment. It may, as in the case of Rucks and Hobson,[6] be useful temporarily in restoring circulatory and respiratory effort. Even in their case, however, the simultaneous use of artificial respiration and a resuscitator makes difficult the evaluation of the adrenalin. In our case, as in the case of Sharkey,[5] no adrenalin was used *; nor did the digifoline, caffeine, or coramine administered prevent the rapid progress of circulatory collapse prior to the use of adrenal cortical extract.

Vitamin K plays no rational part in the therapy. Although occasional small hemorrhages do occur in the liver in cases of Waterhouse-Friderichsen syndrome, and cloudy swelling of the hepatic parenchymal cells, slight cellular infiltrates [11] and distortion of the normal radiating structure [10] have been noted, these are not more marked than in any severe systemic infection without bleeding, and no evidence has yet been adduced that any changes in hepatic function relative to thrombinogen exist. In our case a blood prothrombin time (Quick method) at the height of the clinical bleeding showed a normal figure of 13 seconds (control 12 seconds). Perusal of the case of Rucks and Hobson [6] fails to reveal any convincing clinical evidence that the synthetic vitamin K (Synkamine) used in any way altered the course of the disease. No prothrombin determinations were made in that case.

The dramatic improvement in our patient's condition, the rapid change from cold to warm extremities, and the rapid disappearance of the postmortem-like lividity following the intravenous administration of the adrenal cortical extract (a procedure apparently first suggested by Goldzieher and Greenwald [12] but not used by them) impressed us sufficiently to feel that replacement therapy should be instituted in this manner rather than intramuscularly. The detailed account of Carey's case [2] suggests that he too felt as we do, since first signs of improvement appeared after intravenous rather than intramuscular injection of the extract. On the contrary, Rucks and Hobson,[6] using the intramuscular route, did not obtain so smooth a recovery from the signs of adrenal failure but met with several episodes suggesting recurrent adrenal insufficiency and were forced to shorten very materially the interval between doses of the extract. We believe further that large and probably excessive doses of the adrenal cortical extract should be given intravenously during the critical stages and that these be supplemented by intramuscularly injected extract to maintain through slower absorption the beneficial effects. Of equal importance is the use of large amounts of sodium chloride and of fluids, a regimen fully recognized in the treatment of the crises of Addison's disease. Although no sodium determinations were made in our case during the acute illness, a similar determination in another case (in which, as in the present case, there had been no vomiting) seen shortly before

* The case of Bickel [3] was not available to us. The paper of Grace, Harrison and Davie [4] mentions a case of recovery but cites no details or mode of therapy, the citation being incidental to a general discussion of the syndrome and the report of several fatal cases with autopsy findings.

this one and terminating fatally within one hour after admission to the hospital and before therapy could be instituted, gave a very low value for sodium, 121 meq./L (normal level in this laboratory being 135 to 145 meq./L, by the modified Butler method [13]). This value, as well as a similarly low one cited in the case of Sharkey,[5] the only such studies that seem to have been made in cases of the syndrome, bear out the suggestion of Aegerter [14] that sodium determinations be used as confirmatory evidence of adrenal hemorrhage in suspected cases, a suggestion questioned by Carey [2] who felt that the disease was of too short duration materially to affect the sodium level. Whether any resultant edema may be due to the excessive cortical extract therapy [15] or, as we believe in our case (because of the latent period of development and the simultaneous blood protein changes), is nutritional, is of little moment. In the Waterhouse-Friderichsen syndrome one is dealing with a condition so grave and so rapidly fatal that all other metabolic disturbances are purely secondary, to be dealt with after the patient has been tided over the first few days. In the four previous cases seen by us, death had ensued within 24 hours of onset of symptoms. This statement as to cortical extract therapy does not imply that other symptomatic and shock-combative measures are not to be used. We believe, however, that all these should be subordinate to the adrenal cortical extract and saline therapy. We feel further that it is advisable to continue cortical extract therapy for some time after the disappearance of signs of circulatory collapse, a procedure also followed by Sharkey.[5] Particularly is this important when it is remembered that the infection, localizing in the meninges or serous membranes in other parts of the body or in viscera (such as the heart valves), may remain clinically dormant for several days or longer, only to become clinically active again if chemotherapy is relaxed, a series of events we have seen on several occasions. Should this occur after adrenal cortex replacement therapy already had been discontinued recurrence of the Waterhouse-Friderichsen syndrome might take place even though the evidences of infection be slight. It is for this reason that we continued the sulfadiazine therapy also for seven days, long after all clinical evidence of the infection had vanished save for the continued leukocytosis, the presence in the blood smears of immature leukocytes and toxic granules, and even in the face of a sulfadiazine fever and evidences of renal irritation. The case of Rucks and Hobson [6] illustrates the recurrent phases of the infection and the possibility of recurrences of adrenal insufficiency.

Of interest in our case was the behavior of the peripheral blood cells. So fulminant was the infection that the peripheral blood formula was that of extreme immaturity, a formula that persisted for at least five days after all other evidences of the infection had disappeared. Not until 11 days after the complete clinical subsidence of the infection did the blood picture become approximately normal. Even at this time toxic granules, not present at the height of the infection but appearing as the infection waned, were still present in large numbers. That these changes were not in any way attributable to the sulfadiazine therapy is suggested by the absence of significant changes in erythrocyte or hemoglobin values, and the absence of clinical or laboratory evidences of hemolysis. Whether or not extensive hemorrhages in the bone marrow, found by us in two other cases of the syndrome coming to autopsy, play any part in the blood picture cannot be said.

That the infecting organism did not significantly reach the central nervous

system in our case is suggested by the almost total absence of neurologic signs or symptoms, a finding common to most of the recorded cases of the syndrome.

No substantial reason has yet been advanced for the development of the Waterhouse-Friderichsen syndrome, nor has any complete explanation been given for the occurrence of the massive adrenal, cutaneous, and parenchymal hemorrhages noted in the disease. Schrader [16] and Brunner [17] suggested that thrombosis of the adrenal veins brought about the adrenal hemorrhages, a finding not since reported. It has been suggested [18] that the extraordinary fineness of the adrenal vessel walls in the newborn, associated with venous congestion in the course of difficult prolonged labor, may account for the greater frequency of suprarenal hemorrhage in infants. In infants, it has further been suggested [19] that the adrenal medulla, while undergoing involution, has a rich supply of capillaries and, therefore, readily lends itself to trauma by a variety of agents. Such capillaries and involutional changes do not exist in the adult, for which reason recourse has been had to the theory of selective action of meningococci for structures of ectodermal origin,[19, 20, 21] or the syndrome has been linked with the highly controversial subject of status lymphaticus.[21, 22, 23] As to the former theory of the pathogenesis in adults, no evidence has been presented; as to the latter, there exists, specifically in the cases of the Waterhouse-Friderichsen syndrome, considerable clinical and pathologic evidence to the contrary. This evidence is best presented in the papers of Kunstadter [19] and of Herbut and Manges.[10] It may be that the capillary disorder so long present in our patient and of such marked degree was a factor in causing the massive bleeding noted, that these capillaries, long showing evidence of lowered resistance, broke down under the strain of the severe systemic infection, with the resultant hemorrhages; and that hemorrhages occurring in the adrenals gave rise to the clinical syndrome. The apparent paucity of cases of fulminating purpura of infectious origin, especially in adults, in the face of so many severe septicemic infections, makes probable the presence of some unusual vascular factor, as noted in our case, and should be looked for in future cases that recover from the disease. The factor of reduced capillary resistance persisted in our case though apparently much less pronounced. The last tourniquet test, performed two months after her discharge from the hospital, showed 25 petechial hemorrhages. Concomitantly, the skin lesions noted on the legs for many years disappeared and the urine remained consistently free from red cells since the patient's recovery from the acute infection. We cannot account for this apparent improvement in the state of the capillaries. It may be that the severe shock to the organism improved the capillary tonus in some undetermined manner.

In this year of high incidence of meningococcus infections (for New York City almost as many cases had been reported for the first three months of 1943 as for the entire year of 1942),[24] it is impossible to trace with certainty the source of infection in our case. The only direct contact with the organism that we can determine was a series of cases admitted to the hospital during the months of January and February 1943, the spinal fluids of which our patient examined. She was last in contact with a positive spinal fluid on February 15, 1943, 17 days before she contracted the disease. With the incubation period of the disease so indefinite and ranging from two days to eight weeks, it is manifestly impossible to exclude these contacts. Nevertheless, it should be pointed out that the patient was a very careful technician and a highly skilled bacteriologist,

and one who, despite daily contacts with virulent pathogens over a period of 22 years, had never contracted even the slightest local or systemic infection.

No attempt has been made in this paper to describe the clinical manifestations of the syndrome. Our case followed the conventional pattern. Excellent descriptions and statistical analyses of signs and symptoms have appeared, especially in the reviews of Aegerter,[14] Sachs,[22] and recently of Lindsay and associates.[25] The disease is easily recognizable once seen or kept in mind. Even in cases recognized apparently after an interval and after other diagnoses had been entertained,[8] vigorous adrenal cortical replacement therapy yields clinically encouraging results. In fact, such a case, though terminating fatally, might well have been considered as one of recovery from the Waterhouse-Friderichsen syndrome, death apparently resulting from an intercurrent massive pneumococcal pneumonia that complicated the meningococcemia. In this case also there occurred the only recorded instance of pituitary necrosis. Whether this finding is sufficient to warrant the addition of pituitary hormones to the therapeusis of the syndrome is a matter for future study. Very useful in the diagnosis in doubtful cases is the recognition of bacteria in direct smears from the purpuric eruptions as first suggested by McLean and Caffey [9]; this was done in our case. The value of this simple and rapid procedure is emphasized by the recent pathologic studies of Herbut and Manges.[10]

Although the syndrome has become generally known as that of Waterhouse and Friderichsen,[1] it should be pointed out that the first case, complete with autopsy findings, was reported by Voelcker [26] in 1894, that isolated cases were subsequently reported by numerous authors (noted by Waterhouse, who found 15 cases in the literature up to the time of his own paper in 1911), and that the syndrome seems clearly to have been recognized and associated with adrenal hemorrhage and bacterial infection by Little [27] and by Andrews.[28]

Summary

1. A non-fatal case of fulminating meningococcemic purpura (Waterhouse-Friderichsen syndrome) is reported and the five previously recorded recoveries from the disease are briefly discussed.

2. The rôle of large doses of adrenal cortical extract and saline in the treatment of the disease is stressed. It is suggested that the intravenous route be used during the acute phase and that replacement therapy be continued for some time after improvement in the blood pressure levels. Chemotherapy should be used vigorously, due allowance being made for latent infection and the possibility of recrudescences.

3. It is suggested that neither adrenalin nor vitamin K plays any essential part in the therapy. Adrenalin may be of value as a temporary cardiorespiratory stimulant when cardiac arrest occurs, but is not to be considered as a specific agent because of the adrenal involvement.

4. The rôle of a deficient capillary system, long present in our patient, is pointed out as a possible factor in the pathogenesis of the disease. It is suggested that further cases of recovery be studied from this point of view.

5. A lowering of the blood serum sodium values occurs in the syndrome. It is suggested that this determination may be useful in the differential diagnosis of adrenal damage in cases of infectious purpura.

6. The demonstration of organisms in direct smears from the purpuric areas is stressed as a rapid diagnostic aid.

We should like to express our thanks to Miss Elsie Kaye, Miss Elsie Weidman, and Mr. Alvin Dubin, of the department of pathology, for their painstaking laboratory studies respectively of the hematologic, bacteriologic, and chemical phases of this case.

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Ibid.: A case of acute meningococcal septicaemia, Lancet, 1906, i, 1172.

Since our paper was submitted for publication, eight additional cases of the Waterhouse-Friderichsen syndrome eventuating in recovery have appeared in the literature. All received chemotherapy (sulfadiazine or penicillin) and large amounts of adrenal cortex extract and saline. These cases are recorded in the following papers:

Peabody, S. D.: New England Jr. Med. Sci., 1943, ccxxix, 934 (one case).

Bush, F. W., and Bailey, F. R.: Ann. Int. Med., 1944, xx, 619 (two cases).

Osborne, J., Arnone, W. H., and Lythcott, G. H.: New England Jr. Med. Sci., 1944, ccxxxi, 868 (four cases).

LoVetere, A. A.: Kentucky Med. Jr., 1945, xliii, 24 (one case).

We have ourselves treated two additional identical cases in identical manner save for the substitution of penicillin for sulfadiazine, with uncomplicated recovery.

Bush and Bailey (cited above in note) also confirm the presence of low serum sodium values in cases of the syndrome.

CANDIDA ALBICANS (*MONILIA ALBICANS*) INFECTION WITH BLOOD STREAM INVASION; REPORT OF A CASE WITH A STRAIN CLINICALLY RESISTANT TO SULFONAMIDE DRUGS AND TO PENICILLIN IN VITRO*

By Stanford Wessler, M.D., and Harold R. Browne, M.D.,
Albany, New York

The following case is reported because of renewed wartime interest in fungus diseases and because of the comparative rarity with which Candida has been found in the blood stream.

The ubiquity of human moniliasis is more fully appreciated today than in former years. Keiper [1] concluded that 3 per cent of apparently normal individuals harbor monilia in their throats. Schnoor [2] has commented on the high incidence of monilia in normal stools. Systemic infection is not rare, as evidenced by reports in the literature of involvement of the bone, lungs and parenchymatous organs with this fungus. Despite this fact, however, up to the present time, few cases of blood stream moniliasis have been reported. Only five instances were found in the literature,[3, 4, 5, 6] all occurring in drug addicts, all ending fatally, and all showing mycotic endocarditis at autopsy. In four patients

* Received for publication January 12, 1944.
From the Medical Service, Albany Hospital, Albany, New York.

the organism was identified as *Candida parakrusei,* in the fifth as *Candida guillermondi.*

In the case to be presented, the patient was not an addict, so that the introduction of the fungus into the circulation by hypodermic needle puncture can be excluded. The organism isolated was *Candida albicans,* and instead of a fatal termination, a temporary remission occurred.

Case Report

T. D., a 43 year old white railroad worker, was in fair health until January 6, 1943 when, following exposure to cold and rain, he developed coryza, cough productive of whitish sputum, fever, sweats and malaise. These symptoms continued despite treatment with sulfathiazole and on the second day prior to hospital entry, January 23, were associated with severe dyspnea, orthopnea and wheeze. He had not had chills, chest pains or hemoptysis.

During the preceding 20 years, following acute respiratory infections, the patient had had occasional coughing spells associated with dyspnea. For the last four years the attacks had been more severe and had been accompanied by an audible wheeze. The past history was irrelevant except for "athlete's foot" in 1935 followed by a mild leg infection. The left hand was amputated at the wrist in 1919 after an accident. For the past five years the patient had had marked polydipsia (drinking over 1½ gallons of water per day) and marked urinary frequency (20 times per day). These symptoms were never satisfactorily explained.

The patient's wife had had a non-productive cough for six months.

On admission the patient appeared flushed, dyspneic, orthopneic and was sweating profusely. The temperature was 102° F. The pharynx was diffusely reddened, the tonsils were enlarged and appeared chronically infected. Respirations were shallow, 38 per minute, but there was no splinting. The anteroposterior diameter of the chest was enlarged, and there were sibilant and sonorous râles throughout both lungs. The heart did not appear enlarged; sounds were distant. There was a sinus tachycardia (140 per min.); there were no thrills or murmurs. The abdomen was slightly distended, but no masses or tenderness were noted. The remainder of the examination was negative except for the healed stump of the left arm.

Course: The patient appeared acutely ill on admission and it was thought that he had acute tracheobronchitis. The urine showed 1 plus albumin, 2 plus acetone. The leukocytes numbered 9,100, with 82 per cent neutrophiles, 2 per cent eosinophiles and 16 per cent lymphocytes; the erythrocyte count was 4,630,000; hemoglobin 16.5 grams. Non-protein nitrogen of the blood was 25 mg. per cent.

Several hours after admission the patient was in severe respiratory distress. The vocal cords were edematous, and adrenalin and oxygen were administered with some relief. Twelve hours after entry the patient became increasingly resistant and disoriented, and continued to raise large quantities of thick, tenacious, mucoid sputum. Sodium amytal was given intravenously to quiet the patient.

On the second day, January 24, the admission throat and sputum cultures were found to contain a variety of microörganisms, chiefly pneumococcus type XIX, hemolytic and non-hemolytic streptococci and an unidentified yeast. The patient's temperature was now 103° F. A blood culture was taken and sulfadiazine and fluids were started intravenously. Within 24 hours the patient's temperature and symptoms began to subside; the temperature became normal after 48 hours of chemotherapy and so remained throughout the balance of the hospital stay. Fluid balance was good, satisfactory drug levels were obtained, and by the fifth day (February 28) the patient, except for mild cough, was asymptomatic. Chest films on January 23, January 25

and January 26 (including lateral view) revealed nothing beyond generally and symmetrically increased markings. Repeated urine examinations were negative. The blood examinations remained essentially unchanged.

The blood culture of January 24 yielded 16 colonies per c.c. of a yeast-like microorganism. This microörganism was not immediately identified, but was believed to be a species of Candida. Sputum culture January 26 was also positive for the same microörganism. A blood culture on January 26 yielded 12 colonies per c.c. and a culture on January 28 yielded 22 colonies per c.c., both in 48 hours. Sulfadiazine was continued until the eleventh day, February 2, when a rash developed, and the drug was stopped.

Despite excellent clinical improvement, the following cultures continued to be positive for Candida: blood cultures taken on January 30, February 1; throat cultures taken on February 5; urine cultures made on January 30 and February 7; and a stool culture made on February 4.

Sodium iodide was given intravenously on February 4 and then thymol 0.5 gm. and syrup of hydriodic acid 4 c.c. t.i.d. were started. Blood cultures on February 5 and February 7 were sterile. The patient was discharged on this therapy on February 7, the sixteenth hospital day.

In passing, it may be said that no growth of Candida was noted in blood cultures taken from other patients during the time our patient was in the hospital. A blood culture from one of the patient's neighbors on the ward was sterile on the day our patient's blood was positive.

On February 2 a culture of the fungus was sent to Dr. C. W. Emmons of the U. S. Public Health Service, Bethesda, Maryland. He confirmed the diagnosis of Candida and identified it specifically as *Candida albicans*.

Interval Note: At home the patient continued to take iodides, and eventually returned to work, despite a slight cough. He visited the hospital clinic on February 20, at which time blood, throat and urine cultures were taken. Both throat and urine cultures still yielded *Candida albicans;* the blood culture was negative. At this time, too, the patient's wife submitted to blood and throat cultures, the latter of which yielded the same microörganism. A throat culture from the patient's daughter was also positive for *Candida albicans*.

Second admission: On May 16 the patient entered the hospital for further study. There were no complaints. Urine, blood examination, the Wassermann reaction and the blood non-protein nitrogen were all within normal limits. Stereoscopic views of the chest were negative. A stool on May 17 was positive for Candida. Cystoscopy May 18 revealed the entire bladder floor to be markedly thickened and edematous. Each ureter was catheterized and specimens from each were positive for Candida. Retrograde pyelograms were negative except for slight dilation of the left kidney pelvis and lower calyces. Culture of prostatic secretions was negative. Bronchoscopy May 20 failed to reveal ulceration or stenosis, though there was moderate edema throughout. Secretions were collected for cultural study; these were positive for Candida on June 5. The culture was subsequently suspended in saline and 1 c.c. inoculated intravenously into a rabbit. The animal died nine days later; many abscesses were found in the kidneys, and yeast was recovered culturally from the heart's blood and kidney of the animal. Following completion of this study the patient was discharged May 22.

A culture of *Candida albicans* isolated from the patient's blood in May was studied in October 1943 by Dr. G. L. Hobby, of the Department of Medicine of Columbia University, with particular reference to the action of penicillin in vitro. Dr. Hobby states that this culture is completely resistant to the action of penicillin, which agrees with the results which she has obtained previously with old stock cultures.

Comments

It seems likely that moniliasis of the respiratory tract existed for some years prior to the present illness, in view of the history of coughing spells, dyspnea and wheezing. A mild bronchial asthma, also present, may have been causally related to the fungus infection. Allergic phenomena following moniliasis have been reported by Castellani and others.

The significance of the urinary symptoms, also present for several years, is difficult to evaluate. However, the bladder lesions seen by cystoscopy appeared chronic and probably represented old lesions. If this assumption is correct, it is fair to postulate that in this patient protracted, low-grade hematogenous infection must have occurred, with filtering out of the fungi in the kidneys. Although no lesions could be demonstrated in the kidney, the inflammation in the bladder, coupled with positive ureteral cultures and sterile prostatic fluid, suggest renal moniliasis.

In January 1943 the patient developed a severe bronchitis which, though it responded to chemotherapy, sufficiently lowered his resistance to allow *Candida albicans* to spread through the blood stream. Whether the favorable clinical course was determined by the patient's resistive powers or by the low virulence of the organism is open to speculation. It must, however, be realized that slowly progressive lesions may still exist, which will only become apparent in time.

Apparently the sulfadiazine was effective only against the pyogenic cocci which were present in the respiratory tract. Though the iodides had no effect on the respiratory and urinary tract cultures, it is noteworthy that five blood cultures were positive for Candida before this therapy was instituted, but 24 hours later the blood became sterile and remained so throughout the subsequent course.

It is interesting to consider the significance of the presence of *Candida albicans* in the throats of the patient's wife and daughter. The former had a cough for six months which might have been indicative of pathological changes in the respiratory tract, although studies to establish such changes were not carried out. There is perhaps, some epidemiologic significance in the fact that the patient is employed in the New York Central freight yards at Selkirk, New York. Freight trains and their crews leave from this junction for destinations all over the continent. The possibility of this individual acting as a focus for the dissemination of a pathogenic fungus should be considered.

We can offer no adequate explanation for the rarity of positive blood cultures in cases of Candida infection. It is possible that more frequent culturing of the blood in cases of this sort would demonstrate that the finding is not actually rare.

Summary

This case represents an instance of systemic moniliasis due to *Candida albicans* in which cultures of the microörganism were obtained from the blood, bronchial secretions, pharynx and urine and feces. As far as we know it is the first case recorded in which *Candida albicans* has been demonstrated in the blood stream during life.

Acknowledgment: We wish to express our thanks for their assistance in this study to the following: Dr. C. W. Emmons, U. S. Public Health Service, Dr. Arthur W. Wright, Professor of Pathology and Bacteriology, of the Albany Medical College, Dr. G. L. Hobby, of the Department of Medicine, Columbia University, and Dr. L. W. Gorham, Professor of Medicine, of the Albany Medical College.

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3. WIKLER, A., WILLIAMS, E. G., DOUGLASS, E. D., EMMONS, C. W., and DUNN, R. C.: Mycotic endocarditis, Jr. Am. Med. Assoc., 1942, cxix, 333–336.
4. JOACHIM, H., and POLAYES, S. H.: Subacute endocarditis and systemic mycosis (monilia), Jr. Am. Med. Assoc., 1940, cxv, 205–208.
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6. POLAYES, S. H., and EMMONS, C. W.: Final report on the identification of the organism of the previously reported case of subacute endocarditis and systemic mycosis (monilia), Jr. Am. Med. Assoc., 1941, cxvii, 1533–1534.
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EDITORIAL

THE VIRUS OF LYMPHOGRANULOMA VENEREUM

LYMPHOGRANULOMA venereum is a disease which presents itself in a number of different clinical types. The infection is usually transmitted by sexual contact, and the presenting lesions are generally located in the genital and perineal region. The indolent ulcerating inguinal buboes (climatic buboes, tropical buboes) commonly seen in men, esthiomène with hypertrophy and ulceration of the labia, and the ano-rectal syndrome with proctitis and rectal stricture, were all recognized and described as distinct clinical entities many years ago. That these were merely different manifestations of the same disease was not realized until Frei [1] in 1925 devised his intracutaneous test, utilizing as antigen pus aspirated from inguinal buboes.[2]

A major advance was accomplished when Hellerström and Wassén [3] in 1930 succeeded in isolating the virus. They inoculated pus aspirated from inguinal buboes intracerebrally into monkeys, and produced a meningoencephalitis in these animals. An antigen (like a Frei antigen) prepared from the brain tissues of such monkeys caused a positive intracutaneous reaction in human patients who reacted positively to the Frei test. This work has been repeatedly confirmed. The infection has been maintained by serial inoculations in monkeys and also in mice which are likewise highly susceptible to intracerebral inoculation. Lesions have also been produced less regularly by intracutaneous, intracorneal and intraperitoneal inoculations, and other laboratory animals can be infected, but the mouse appears to be the most satisfactory. By this method the virus has been obtained and identified from a variety of human lesions, including the small initial ulcer ("chancre"), the inguinal buboes, the labial tissue in esthiomène, the rectal mucosa, the urethra and cervix, from conjunctival exudates, and from the spinal fluid in cases with meningitis. This is the only procedure which furnishes conclusive proof of the nature of a suspected lesion.

Infection in man may occur by other routes, as through the skin (of the finger, with secondary involvement of the axillary lymph nodes), through the mouth, and probably the respiratory tract. The virus is not limited to the conspicuous local lesions, but it may become generally disseminated. The disease may run the course of an acute systemic infection, as in the cases of accidental infection of laboratory workers reported by Harrop.[4]

[1] FREI, W.: Eine neue Hautreaktion bei Lymphogranuloma inguinale, Klin. Wchnschr., 1925, iv, 2148.

[2] For an excellent general review, see: KOTEEN, H.: Lymphogranuloma venereum, Medicine, 1945, xxiv, 1–69.

[3] HELLESTRÖM, S., and WASSÉN, E.: Meningo-enzephalitische Veränderungen bei Affen nach intracerebraller Impfung mit Lymphogranuloma inguinale, Verhandl. 8te Internat. Kongr. Dermat. u. Syph., 1930, 1147.

[4] HARROP, G. A., RAKE, G. W., and SHAFFER, M. F.: New clinical conceptions of lymphogranuloma venereum, Trans. Assoc. Am. Phys., 1941, lvi, 101.

Many other lesions have been attributed to this virus on the basis of a positive Frei test, or because of the production of a positive intracutaneous test with antigen prepared from suspected lesions, carried out on other individuals who give a positive Frei reaction. This procedure is often referred to as an "inverted Frei test." Its complete dependability as proof that a lesion is caused by the virus of lymphogranuloma inguinale is not as yet generally accepted.

The virus is filtrable through the filters usually employed, and according to Findley it is from 0.125 to 0.175 micron in diameter. Like other viruses it can not be cultivated on ordinary media, but grows only in living cells. It has been grown in tissue cultures and on the chorioallantoic membrane of an embryo chick. Rake et al.[5] found that it will grow luxuriantly in the yolk sac of the chick embryo, and this has proved a valuable method of obtaining uncontaminated virus in large quantities. This has largely replaced other materials in preparing virus for the Frei test. It has also provided favorable conditions for studying the morphology of the virus.

Several earlier observers described inclusion bodies in the cells of infected exudates, notably in monocytes, which they believed represented the virus. Findley et al.[6] described them in greater detail as seen in the brain cells of infected mice, and believed that they could trace a developmental cycle of the virus. Rake et al.[7] have confirmed this by a study of infected chick embryo yolk sacs. Following inoculation of the yolk sac, for some hours they were unable to detect virus microscopically except the elementary bodies contained in the inoculum. These were minute structures which took a reddish color with their differential stain and appeared to be about 0.4 micron in diameter. After about 12 hours, "initial bodies" were seen in small numbers inside the cells. They appeared first as isolated structures about 1 micron in diameter, near the cell membrane. Later they appeared in pairs, tetrads, and small groups. They stained a greenish color. The groups became segregated within small vesicles in the cell cytoplasm, surrounded by a limiting membrane (possibly a defense mechanism of the invaded cell) and embedded in a greenish staining matrix. These bodies increased in size up to a diameter of 4 to 7 micra, and then began to show differentiation in internal structure. Minute red-staining elementary bodies about 0.4 micron in diameter appeared, together with small vacuoles, from which the authors believed elementary bodies had escaped. The cell might then rupture, liberating the elementary bodies which then might enter into fresh cells and start another similar cycle of development; or the formation of elementary bodies might continue until the vesicle practically filled the entire cell. This

[5] RAKE, G., MCKEE, C. M., and SHAFFER, M. F.: Agent of lymphogranuloma venereum in yolk sac of developing chick embryo, Proc. Soc. Exper. Biol. and Med., 1940, xliii, 332.

[6] FINDLEY, G. M., MACKENZIE, R. D., and MACCALLUM, F. O.: A morphological study of the virus of lymphogranuloma inguinale (Climatic Bubo), Trans. Roy. Trop. Med. and Hyg., 1938, xxxii, 183.

[7] RAKE, G., and JONES, H. P.: Studies on lymphogranuloma venereum. I. Development of the agent in the yolk sac of the chick embryo, Jr. Exper. Med., 1942, lxxv, 323.

process went on until at the death of the embryo substantially every cell of the yolk sac might be involved. The infective titer of the contents of the yolk sac rose in parallel with the observed increase in virus bodies.

This process as described by Rake resembles that reported in inclusion blennorrhea and trachoma, and particularly the cycle in psittacosis as described in the spleen of infected mice by Bedson and Bland [8] and by many subsequent observers.

The virus of lymphogranuloma induces specific immune reactions in infected animals and human beings. The Frei test is a manifestation of a local immune or allergic reaction. This may become positive within a week after infection and usually does so within three weeks, but occasionally only after three months. In a small percentage of cases it fails to develop ("anergy"). Although the reliability of the test is questioned by some observers, the consensus of opinion is that if properly performed it has a high degree of specificity. An individual who has once given a positive reaction will usually continue to do so indefinitely. A few cases of reversion, however, have been reported after effective chemotherapy.

Along with cutaneous hypersensitiveness, antibodies appear in the serum. The most significant manifestation of this is the capacity of the serum specifically to neutralize the virus. This was demonstrated by Levaditi, and has been used by Findley and others to demonstrate the etiology of peculiar or unusual lesions. Complement fixation reactions may also be obtained. McKee and associates,[9] using as antigen virus obtained from the yolk sac of infected chick embryos, obtained positive reactions in a very large proportion of clinical cases of lymphogranuloma venereum. This seems to be at least as sensitive as the Frei reaction, and to be highly specific, although its dependability is not so thoroughly established. Harrop [4] regards a titer of 1–6 as diagnostic. A significant percentage of patients in venereal disease clinics, without clear clinical evidence of lymphogranuloma venereum, give positive complement fixation reactions and also often positive Frei reactions. There is good reason to believe that at least a large proportion of these are cases of latent infection with lymphogranuloma venereum virus.[4] None of these immune reactions, however, prove the nature of a presenting lesion. They merely indicate that the individual has at some time acquired the infection, and the current illness may be due to an entirely different agent.

Furthermore, the virus of lymphogranuloma venereum is related antigenically to that of psittacosis and to other viruses of the "psittacosis group," including trachoma, inclusion blennorrhea, meningo-pneumonitis of Francis and Magill, and viruses obtained from certain cases of atypical pneumonia. All of these viruses and their specific antisera exhibit cross-reactions with one

[8] Bedson, S. P., and Bland, J. O. W.: Developmental forms of psittacosis virus, Brit. Jr. Exper. Path., 1934, xv, 243.

[9] McKee, C. M., Rake, G., and Shaffer, M. F.: Complement-fixation test in lymphogranuloma venereum, Proc. Soc. Exper. Biol. and Med., 1940, xliv, 410.

another in greater or less degree. Levine et al.[10] reported positive complement fixation reactions, using lymphogranuloma venereum antigen, in 11 cases of pneumonia caused by these viruses, although in the three cases showing the highest titer, the Frei reaction was negative. Rake, however, has reported false positive Frei reactions in some cases of atypical pneumonia. Clinically, the differentiation of these cases from lymphogranuloma venereum would usually be simple.

Rake and Jones[11] have recently reported experiments which indicate the presence of a toxic agent in suspensions of lymphogranuloma venereum virus, and also of the related viruses of meningo-pneumonitis, mouse pneumonitis and feline pneumonitis. After injections of relatively huge doses intravenously into mice, the animals died acutely, usually within four to 24 hours, and showed visceral lesions which they interpreted as the result of toxic degeneration rather than infection. They regarded the toxic substance as analogous to bacterial endotoxins. It was intimately associated with the elementary bodies in the suspensions. It was very labile, and they were unable to render the virus noninfective without destroying the toxin. By repeated injections into rabbits and chickens they obtained sera which neutralized a few m.l.d. of the toxin. Serum from patients with lymphogranuloma venereum exerted a similar antitoxic action. The antitoxic action of their immune sera, under the conditions of their experiments, was highly specific and limited to the homologous type of virus. The sera did not show cross-reactions with other viruses of the group, noted with complement fixation and ordinary virus neutralization tests. They suggested that this toxin neutralization may prove more useful in differentiating these closely related viruses than the serological procedures which have usually been employed.

The virus of lymphogranuloma venereum differs from most other viruses in being in some degree susceptible to the sulfonamide drugs. According to Rake et al.[12] several other viruses of the psittacosis group are also susceptible to sulfonamides. Their clinical value in the treatment of patients with lymphogranuloma venereum is generally recognized. Sulfonamides will prevent the death of mice experimentally infected by intracerebral inoculation of this virus. These animals, however, may present mild symptoms of infection. Examination of the brain showed cellular infiltrations which might be substantially equal to those in untreated and fatally infected mice. The brain tissue of such "cured" mice on inoculation into other mice or into chick embryos caused infection in them. The sulfonamides, there-

[10] Levine, S., Hilder, E. C., and Bullova, J. G. M.: Complement fixation for lymphogranuloma venereum and for psittacosis with Frei reaction among pneumonia patients, Jr. Immunol., 1943, xlvi, 183.

[11] Rake, G., and Jones, H. P.: Studies on lymphogranuloma venereum. II. The association of specific toxins with agents of the lymphogranuloma-psittacosis group, Jr. Exper. Med., 1944, lxxix, 463.

[12] Rake, G., Jones, H. P., and Nigg, C.: Sulfonamide chemotherapy of mouse pneumonitis, meningo-pneumonitis and lymphogranuloma venereum, Proc. Soc. Exper. Biol. and Med., 1942, xlix, 449.

fore, exert a virostatic rather than a virocidal action. They suppress the clinical manifestations of infection and possibly induce a chronic carrier state, rather than effect a fundamental cure.

It seems likely that the same may be true in the case of human infection. The persistence of a positive Frei reaction in many treated cases suggests this. There is as yet no assurance that these cases are not infectious or that they may not relapse. Manifestly a great deal more study of these problems is needed.

In spite of many gaps in our knowledge, much has been accomplished toward clearing up the problem of lymphogranuloma venereum, with the isolation of the virus, its cultivation in the chick embryo, the development of reliable diagnostic procedures and the discovery of a reasonably effective therapy. This is of practical importance, since it is now known that the disease is relatively common among sexually promiscuous individuals, at least in the Southern States and on the Eastern Seaboard. These studies are also of theoretical interest in showing that the virus of lymphogranuloma venereum and the various viruses of the "psittacosis group" possess many distinctive features in common, which serve to separate them quite sharply from the other filtrable viruses.

REVIEWS

Embryology of Behavior. By ARNOLD GESELL, M.D. 289 pages; 23.5 × 16 cm. 1945. Harper & Brothers, New York. Price, $5.00.

The author has compiled a number of very interesting observations "to indicate how an organic complexus of behavior is built up concomitantly with the bodily development of embryo, fetus and neonate." The observations are accompanied by extremely interesting photographic studies of the embryos. One complete section of the book contains many chronological, behavior photographs titled, "A Photographic Delineation." Philosophical deductions, treatises and similar works are frequently cited, with especial favor being shown to Darwin, to substantiate various conclusions.

Dr. Gesell writes in his usual style, proving himself a worthy opponent of H. L. Mencken in word choice. The subject matter is unique and interesting. The photographs are clear and illustrative. The book can be recommended for biologists, pediatricians and possibly obstetricians. It has no use for parents other than those fully acquainted with medical terminology.

J. E. B.

BOOKS RECEIVED

Books received during April are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Penicillin Therapy, Including Tyrothricin and Other Antibiotic Therapy. By JOHN A. KOLMER, M.S., M.D., Dr.P.H., Sc.D., LL.D., L.H.D., F.A.C.P. 302 pages; 22 × 15 cm. 1945. D. Appleton-Century Company, New York. Price, $5.00.

The Examination of Reflexes. A Simplification. By ROBERT WARTENBERG, M.D. Foreword by FOSTER KENNEDY, M.D. 222 pages; 18.5 × 12.5 cm. 1945. The Year Book Publishers, Inc., Chicago. Price, $2.50.

Trauma in Internal Diseases. With Consideration of Experimental Pathology and Medicolegal Aspects. By RUDOLF A. STERN, M.D. Foreword by FRANCIS CARTER WOOD, M.D. 575 pages; 23.5 × 15.5 cm. 1945. Grune & Stratton, Inc., New York. Price, $6.75.

Constitution and Disease. Second Revised Edition. Applied Constitutional Pathology. By JULIUS BAUER, M.D. 247 pages; 22 × 15 cm. 1945. Grune & Stratton, Inc., New York. Price, $4.00.

Doctors at War. Edited by MORRIS FISHBEIN, M.D. 418 pages; 24 × 16.5 cm. 1945. E. P. Dutton & Company, Inc., New York. Price, $5.00.

The New-Born Infant. A Manual of Obstetrical Pediatrics. Third Edition, thoroughly revised. By EMERSON L. STONE, M.D. 314 pages; 20.5 × 14 cm. 1945. Lea & Febiger, Philadelphia. Price, $3.25.

Bronchial Asthma. By LEON UNGER, B.S., M.D., F.A.C.P. Introduction by MORRIS FISHBEIN, M.D. 724 pages; 25 × 16 cm. 1945. Charles C. Thomas, Springfield, Illinois. Price, $9.00.

The Rockefeller Foundation. A Review for 1944. By RAYMOND B. FOSDICK, President of the Foundation. 63 pages; 23 × 15.5 cm. 1945. The Rockefeller Foundation, New York.

COLLEGE NEWS NOTES

Enlistments and Discharges, A. C. P. Members

Dr. Alexander McCausland (Associate), Blacksburg, Va., has been commissioned a Lieutenant (j.g.) in the U. S. Navy. This brings the total number of College members who have entered upon military duty to 1,858.

The following members of the College have been honorably discharged:

William R. Galbreath, Major, (MC), AUS—New Orleans, La.
Wendell Charles Hall, Major, (MC), AUS—Hartford, Conn.
Lorenzo Dow Massey, Major, (MC), AUS—Osceola, Ark.
Paul R. Meyer, Captain, Army Air Corps—Port Arthur, Tex.

Oral Examinations American Board of Internal Medicine

Oral examinations by the American Board of Internal Medicine were held at New Orleans, May 21–22–23; at Philadelphia, June 6–7–8. They will be held in Chicago, June 27–28–29 and in San Francisco, October 15–16–17. The examinations at San Francisco are intended for candidates from Arizona, California, Colorado, Idaho, Montana, Nevada, New Mexico, Oregon, Utah, Washington and Wyoming. The closing date for registering for the San Francisco examination is September 1.

Write for application form to the American Board of Internal Medicine, 1301 University Ave., Madison 5, Wisconsin.

Gifts to the College Library

The following gifts of publications by members are gratefully acknowledged:

Books

John A. Kolmer, F.A.C.P., Philadelphia, Pa.—an autographed copy, "Penicillin Therapy," D. Appleton-Century Company.
Franklin B. Peck, F.A.C.P., Indianapolis, Ind.—a bound volume, No. 3, 1944 complete, "Diabetes Abstracts."
Benjamin Saslow, F.A.C.P., Newark, N. J.—"Manual of the Diabetic Clinic," Presbyterian Hospital of Newark.
Peter J. Steincrohn, F.A.C.P., Hartford, Conn.—"Forget Your Age."

Also acknowledged is a gift from the National Research Council, Division of Medical Sciences, "Primate Malaria."

Reprints

M. Meredith Baumgartner, F.A.C.P., Lieutenant Commander, (MC), USNR—1 reprint.
C. Wesley Eisele, F.A.C.P., Chicago, Ill.—1 reprint.
Cecil M. Jack, F.A.C.P., Decatur, Ill.—1 reprint.
Harry Parks (Associate), Atlanta, Ga.—1 reprint.
Frank B. Queen, F.A.C.P., Lieutenant Colonel, (MC), AUS—1 reprint.
Milford O. Rouse, F.A.C.P., Dallas, Tex.—2 reprints.

Sidney Scherlis (Associate), Captain, (MC), AUS—1 reprint.
Bernard M. Scholder, F.A.C.P., Lieutenant Commander, (MC), USNR—1 reprint.
James S. Sweeney, F.A.C.P., Colonel, (MC), AUS—1 reprint.

Captain James Graham Bruce, (MC), AUS Liberated from Bataan

Captain James Graham Bruce, (MC), AUS was among three members of the American College of Physicians who were rescued at Manila during General MacArthur's invasion of the Philippines. The other two were Lieutenant Commander William M. Silliphant, (MC), USN, and Lieutenant Commander J. La Monte Zundell, (MC), USN.

Temporarily, Captain Bruce's address is 24 Hooker Ave., Poughkeepsie, N. Y. After his medical survey at the Lovell General Hospital, Fort Devens, Mass., we understand he will be given a leave of absence and will then be assigned to special work in internal medicine.

Lieutenant M. Leonard Gottlieb, a Prisoner in Japan

Lieutenant M. Leonard Gottlieb, (MC), USNR, an Associate of the College, has been a prisoner of the Japanese since the early part of the war. Word has been received that he has been transferred from the Zentsuji War Prison Camp to Camp Shinagawa in Tokyo. The last direct word from Lieutenant Gottlieb was written during December, 1943, arriving here in February, 1945. His earlier letter stated that the Japanese had given the American doctors some medical books and allowed them to form a medical society of American and British physicians, and permitted them to have some scientific conferences.

Report from the Office of the Surgeon General, U. S. Army

The 5th Annual Meeting of the Army Epidemiological Board was held April 26–27 at the Office of The Surgeon General. The meeting was presided over by Dr. Francis G. Blake, F.A.C.P., Dean of Yale University School of Medicine, New Haven, Conn., who is Civilian Consultant to the Secretary of War and President of the Board.

The Epidemiological Board is administered by the Preventive Medicine Service, Office of The Surgeon General. It consists of a Central Board and ten Commissions: on Acute Respiratory Diseases, Air-Borne Infections, Epidemiological Survey, Hemolytic Streptococcal Infections, Influenza, Measles and Mumps, Meningococcal Meningitis, Neurotropic Virus Diseases, Pneumonia, and Tropical Diseases. The work of these Commissions, however, is not limited to the field indicated by the name, but is authorized according to opportunities, facilities and specialties of members.

During the past year extensive epidemiological investigations have been conducted in this country and in several theaters of operations overseas. This work has not only proved of practical value to the Army, but has materially increased the fundamental scientific knowledge of the causes and control of infectious diseases among the civilian as well as the military population.

Major General Merritte W. Ireland, F.A.C.P., USA, Retired, who modernized the Army Medical Department when he became Surgeon General after World War I, recently received a citation from the Medical Society of the District of Columbia for distinguished services to humanity and military medicine.

The ceremony was attended by the present Surgeon General of the Army, Major General Norman T. Kirk, F.A.C.P., distinguished medical officers from the Army, Navy and Public Health Service, and other prominent physicians and scientists.

General Ireland, who was born 78 years ago in Columbia City, Ind., was graduated from the Detroit College of Medicine and Surgery in 1890, served as Chief Surgeon of the AEF in France during World War I, and as Surgeon General of the U. S. Army from 1918 to 1931. Previous honors accorded him include the William Freeman Snow Medal, the U. S. Distinguished Service Medal, Companion of the Order of the Bath (Great Britain), Commander of the Legion of Honor (France), the Serbian Red Cross Silver Medal and the Polish Polonia Restituta.

Brigadier General Hugh J. Morgan, F.A.C.P., Director of the Medical Consultants Division, Office of The Surgeon General, recently returned from overseas after ten weeks of duty in the European and Mediterranean theaters of operations where he has been inspecting medical installations and conferring on medical problems pertinent to those theaters.

Colonel William C. Menninger, F.A.C.P., Chief Consultant in Neuropsychiatry to The Surgeon General, presided at a conference of Service Command Consultants in Neuropsychiatry at The Surgeon General's Office, April 20–21.

General subjects on the program included induction centers, hospitalization problems, reconditioning, clinical psychology, psychiatric social workers and assistants, mental hygiene consultation services, neurology, disciplinary barracks and rehabilitation centers, school of military neuropsychiatry, preventive psychiatry, personnel, nomenclature, redeployment, history, and public relations.

Among Consultants in Neuropsychiatry in the Army are Lieutenant Colonel Clarke H. Barnacle, F.A.C.P., Seventh Service Command; Colonel Franklin G. Ebaugh, F.A.C.P., Eighth Service Command; and Lieutenant Colonel Lauren H. Smith, F.A.C.P., Ninth Service Command. Dr. Edward A. Strecker, F.A.C.P., Philadelphia, Pa., is one of the Civilian Consultants to The Surgeon General.

Colonel Irving S. Wright, F.A.C.P., has been transferred as Consultant in Medicine from the Sixth Service Command to the Ninth Service Command; Colonel Alexander Marble, F.A.C.P., former Chief of Medical Service, Harmon General Hospital, is now Medical Consultant, Sixth Service Command; Lieutenant Colonel Worth B. Daniels, F.A.C.P., is now Chief of Medical Service at Harmon General Hospital, Longview, Tex.

Lieutenant Colonel Burgess L. Gordon, F.A.C.P., has been appointed Chief of the Medical Service at the new Army General Hospital at Camp Pickett, Va. He was formerly Assistant to the Chief of the Administration branch, Hospital Division, Office of The Surgeon General.

The Harmon General Hospital has been designated for the treatment of tropical diseases. The only other such Army center is the Moore General Hospital at Swannanoa, N. C. Colonel G. V. Emerson, F.A.C.P., is the Commanding Officer.

Educational Opportunities for Army Doctors

Since the start of World War II, over 6,000 selected medical officers have been graduated from short but intensive courses given by the Medical Department in some thirty critical medical and surgical specialties, according to Major General George F.

Lull, F.A.C.P., Deputy Surgeon General. In addition, refresher courses in general medicine and surgery provide medical officers with a chance to "brush up" before returning to professional assignments after other duty.

Many doctors also benefit while in service from working under key professional personnel in military hospitals. Other medical officers who have been on duty with combat troops in the field are given an opportunity to brush up on their specialty through the rotation policy.

General Lull reported that 350 doctors have been reassigned from field to hospital duty during the past year in the Mediterranean Theater and "the merit of intra-theater rotational plans has been pointed out to other theaters, and is being encouraged in order that the maximum number of doctors might receive refresher training while they are still in military service."

Naturally, professional training of medical corps officers during military service must be restricted to meet military rather than civilian requirements. However, General Lull said The Surgeon General is keenly interested in the welfare of these doctors and will provide "insofar as is possible" opportunities for professional training.

In the post-war period, he added, all doctors will be entitled to professional training, after their release from service, under the G. I. Bill of Rights, and those who remain in the Army will have the opportunity for refresher training at selected military hospitals and civilian schools.

Promotions in the Army Medical Corps

From Colonel to Brigadier General:

George R. Callender, F.A.C.P., Everett, Mass.
W. Lee Hart, F.A.C.P., York, S. C.

From Lieutenant Colonel to Colonel:

Eugene Charles Eppinger (Associate), Brookline, Mass.
Edwin Gabriel Faber, F.A.C.P., Tyler, Tex.
Edwin Matthew Goyette (Associate), Burlington, Vt.
William Donald Graham (Associate), St. Paul, Minn.
Gilbert Henry Marquardt, F.A.C.P., Chicago, Ill.
Johnson McGuire, F.A.C.P., Cincinnati, Ohio
Carl Alfred Schuck (Associate), St. Louis, Mo.
Joseph Bedford Vander Veer (Associate), Philadelphia, Pa.

From Major to Lieutenant Colonel:

Maurice James Abrams, F.A.C.P., Brewton, Ala.
Eric MacMillan Chew, F.A.C.P., Mercer Island, Wash.
Adam James French (Associate), Ann Arbor, Mich.
Edward Alfred Greco, F.A.C.P., Portland, Maine
Paul Victor Hamilton, F.A.C.P., Cincinnati, Ohio
Hugh Edward Kiene (Associate), Providence, R. I.
Frederick Lemere, F.A.C.P., Seattle, Wash.
Thomas Wilson Martin (Associate), Pittsburgh, Pa.
Theodore John Pfeffer, F.A.C.P., Racine, Wis.
Herbert William Rathe, F.A.C.P., Waverly, Iowa
Kenneth McLane Smith (Associate), Columbus, Ohio
Walter Maximilian Solomon, F.A.C.P., Shaker Heights, Ohio
Joseph Blackburn Stevens (Associate), Greensboro, N. C.

Dr. Joseph S. Evans, Acting Governor for Wisconsin

Dr. Joseph S. Evans, F.A.C.P., Professor of Medicine at the University of Wisconsin, has been appointed the Acting Governor of the College for Wisconsin during the absence of Dr. Elmer L. Sevringhaus while on a mission to Italy.

Lieutenant Colonel Zacharias Bercovitz, F.A.C.P., formerly of New York City, is now Chief of the Medical Service of a large Army hospital in Assam, India.

Colonel Benjamin J. Birk, (MC), AUS, Milwaukee, Wis., is now on duty in China. He was recently awarded the Legion of Merit Medal "for exceptionally meritorious conduct in the performance of outstanding services." For a period of time, Colonel Birk was commanding officer of a hospital troop ship. He then went to India in February, 1944, and in April of that year was flown over the Himalayan "Hump" to China and has served as medical officer with an American liaison group attached to Chinese combat forces in the fighting about Kweilin, Changsha, Hengyang, Chaun Shien and Luichow.

Lieutenant Commander George F. Schmitt, Jr., F.A.C.P., formerly of Rochester, Minn., and now serving in the U. S. Naval Reserve, has compiled a diet formulary which has been printed and circulated by the Navy's medical department. The formulary is condensed in 102 pages and includes diets, caloric contents of various foods, heights-weights table for men and women and other information concerning diets.

Major John B. Levan, F.A.C.P., formerly of Reading, Pa., has been Chief of the Cardiovascular Section at the McCloskey General Hospital (4,000 bed capacity) since September, 1942.

Dr. Robert S. Berghoff, F.A.C.P., President-Elect of the Illinois State Medical Society, was recently elected President of the Staff of Mercy Hospital, Chicago. Mercy Hospital is the oldest hospital in Illinois, established in 1850, ninety-five years ago.

Dr. J. C. Geiger again Decorated

His Royal Majesty, Haakon, The King of Norway, has conferred upon Dr. J. C. Geiger, F.A.C.P., San Francisco, through the Minister of Foreign Affairs of Norway, the Right Honorable Trygve Halvdan Lie, head of the Norway Delegation at the UNCIO Conference, the Order of St. Olaf, First Class. This order was established in 1847 by Oscar, 1st, in honor of St. Olaf, the founder of Christianity in Norway. The decoration carries with it an Honorary Knighthood and the following citation: "For valuable and distinguished service to Norway in World War II, and for unswerving devotion and intelligent administration of public health in order that human lives be preserved and the world made a better and happier place to live."

Dr. Kendall A. Elsom, F.A.C.P., now Lieutenant Colonel, (MC), AUS, is Chief of Medical Service at the Fort Benning Regional Hospital, Ga.

The Southeastern Regional Medical Conference of the Army Air Forces was held April 23–24 at the AAF Tactical Center, Orlando, Fla. Chairmen at the

various sessions included Lieutenant Colonel Harold F. Robertson, F.A.C.P., Lieutenant Colonel J. F. Painton, F.A.C.P., and Lieutenant Colonel Albert W. Wallace, F.A.C.P.

Among members of the College participating on the scientific program were:

Colonel Donald D. Flickinger (Associate), "Medical Experiences in C.B.I. Theater of Operations";
Dr. Francis F. Borzell, F.A.C.P., Chairman of the War-Time Graduate Medical Meetings Committee, Philadelphia, "Relation of Roentgenology to Internal Medicine";
Colonel W. Paul Holbrook, F.A.C.P., Office of the Air Surgeon, Washington, and Major Arie van Ravenswaay (Associate), "Recent Epidemic of Type 17 Sulfonamide Resistant Hemolytic Streptococci";
Lieutenant Colonel Harold F. Robertson, F.A.C.P., et al., "Early Physical Activity During Acute Rheumatic Fever";
Lieutenant Colonel Albert W. Wallace, F.A.C.P., "Streptococcus Pneumonia";
Dr. Simon S. Leopold, F.A.C.P., Philadelphia, "Chest Pains";
Lieutenant Colonel J. F. Painton, F.A.C.P., "The Electrocardiographic Findings in Primary Atypical Pneumonia";
Captain William M. Sheppe, F.A.C.P., (MC), USNR, "Primary Atypical Pneumonia and Its Complications";
Dr. James S. McLester, F.A.C.P., Birmingham, "Diseases of Nutrition";
Lieutenant Colonel Paul K. French, F.A.C.P., "Infectious Mononucleosis";
Lieutenant Colonel Robert J. Needles, F.A.C.P., "Peptic Ulcer versus Functional Indigestion."

A. C. P. Regional Meeting Held at Buffalo, May 12

Under the Governorship of Dr. Nelson G. Russell of Buffalo and the able assistance of Dr. Roy L. Scott, F.A.C.P., Chairman of Arrangements, a limited regional meeting of the College for Western New York was conducted at Buffalo on May 12. As guests, Fellows of the College from Ontario were invited and several were in attendance.

The morning session was held at the New York State Institute for the Study of Malignant Diseases. Dr. W. H. Wehr and his associates presented the program and conducted the group through the Pathological and X-ray Departments.

Luncheon was served in the solarium of the Buffalo General Hospital, after which the following program was given:

"Observations in Neurocirculatory Asthenia"—Mandel E. Cohen, M.D., Boston;
"Vitamin Deficiency in Tuberculosis"—David K. Miller, M.D., Buffalo;
"Acute Diarrheal Diseases: A Note on Effect of Streptomycin in Typhoid Fever"—Hobart A. Reimann, M.D., F.A.C.P., Philadelphia;
"Somatic Pain—Diagnostic and Therapeutic Aspects of Local Infiltration"—Bernard D. Judovich, M.D., Philadelphia;
"Treatment of Hyperthyroidism with Thiouracil"—George F. Koepf, M.D., Buffalo.

In the evening a reception and dinner were held at the Saturn Club. Mr. Edward R. Loveland, Executive Secretary of the College, addressed the dinner meeting on the "Activities and Objectives of the College and Its Plans for the Immediate Future."

The scientific program was noteworthy and the attendance was exceedingly good—the great majority of the members of the College from the western half of New York were in attendance.

Government Building New Hospital, George Washington University

Announcement was recently made that Dr. Walter A. Bloedorn, F.A.C.P., Dean of George Washington University School of Medicine, has been appointed Medical Director of the new George Washington University Hospital, which is being built by the federal government for the use of the University to meet the needs of the war-time emergency in Washington. The new hospital will have a capacity of 400 beds and will be equipped and managed as a teaching hospital.

U. S. Pharmacopeial Convention Acquires New Headquarters in Philadelphia

The Board of Trustees of the U. S. Pharmacopeial Convention has recently purchased temporary headquarters at 4738 Kingsessing Ave., Philadelphia. Heretofore the Pharmacopeial Revision Chairman has maintained quarters in the building of the Philadelphia College of Pharmacy and Science, but the increasing volume of work has necessitated larger accommodations.

Governor Dewey, New York, Vetoes Bills Recognizing Unaccepted Medical Schools

Governor Dewey of New York recently vetoed two bills which had been passed by the New York Legislature permitting the granting of medical license to graduates of any medical school in the United States. If these bills had been permitted to stand, it is believed that diploma mills and all sorts of substandard schools of medicine would have been revived and all that has been accomplished in the past years in maintaining high standards of recognized medical schools would have been temporarily lost.

Commander Thomas D. Martin, F.A.C.P., (MC), USNR, formerly of Tampa, Fla., received the following citation, as recommended by Admiral C. W. Nimitz recently: "For meritorious and efficient performance of duty as chief of medical service at a fleet hospital in the South Pacific area from May 21, 1943 to March 25, 1944. During this period Commander Martin displayed exceptional professional skill in handling the many medical problems which arose. Through his organizational ability and thorough indoctrination of the medical officers and nurses under his supervision he contributed materially to the efficient administration of the hospital to which he was attached. His initiative and leadership were in keeping with the highest traditions of the naval service."

Dr. David P. Barr, F.A.C.P., New York, acted as Chairman of a Symposium on Peptic Ulcer before a regional meeting of the American Society for Research on Psychosomatic Problems on May 11.

The University of Texas Medical Branch, Galveston, recently announced the founding of a research fellowship in internal medicine in honor of Dr. Marvin Lee Graves, F.A.C.P., Emeritus Professor of Internal Medicine. Funds were donated by Dr. Graves' children in his honor. The fellowship will be filled annually by the Department of Medicine "through the appointment of a graduate in medicine who is considered most likely to maintain the professional standards and ideals of Dr. Graves," according to the announcement.

Dr. George M. Decherd, Jr., F.A.C.P., Associate Professor of Internal Medicine at the University of Texas Medical Branch, Galveston, will direct a new postgraduate medical training program there. It is proposed that the program will embody short postgraduate conferences and courses on special subjects, two-day conferences given by the faculty in coöperation with county and district medical societies over the state, and residency training for specialty board certification and specialty practice.

The Commonwealth Fund has appropriated $8,200 to be used by Dr. Carl J. Wiggers and associates of the Department of Physiology for continuance of their studies on the peripheral circulation and shock during 1945–46.

Dr. Lawrence Parsons, F.A.C.P., of Reno, Nevada, addressed (by invitation) the Sacramento Society for Medical Improvement (Sacramento, California, County Medical Society) on April 17, 1945. He spoke on Relapsing Fever at Lake Tahoe, California-Nevada. Lantern slides of photomicrographs of blood films showing the causative organism, *Borrelia recurrentis* and specimens of the tick transmitters, *Ornithodorus hermsi* and *O. parkeri* were presented. Lake Tahoe is an important endemic focus of relapsing fever in California since, in normal times, large numbers of visitors from all parts of the United States go there, occasionally contract the disease and often prove to be perplexing diagnostic problems upon their return home, particularly in the East.

During the last three years, diphtheria has broken all bounds in Northern and Central Europe and thus become the leading epidemic disease, according to the Epidemiological Information Bulletin No. 4 issued by UNRRA's Health Division. Fifteen years ago diphtheria was at about the same level all over Europe. Up to 1940 it was steadily reduced in most countries, but in Germany it began to increase. From 49,000 cases in 1927 the number of cases reported in the original territory of the Reich increased to 238,400 in 1943. In Norway, on the contrary, there were only 17 cases during the last six months before the German invasion.

The reduction of diphtheria among most of Germany's small neighbors had been brought about without systematic immunization, and the population was therefore not properly protected. This situation was all the more dangerous since a virulent type of diphtheria, not yielding to serum treatment, had spread in Germany. From 3.5 per cent in 1938 the proportion of fatal cases rose to over 6 per cent in 1943. Cases among adults became frequent, and diphtheria appeared in the German army even as a fatal complication of chest wounds.

With the invasion came diphtheria carriers, and explosive epidemics soon appeared in Norway, the Netherlands, Belgium, northern France and Czechoslovakia. In the course of the three last years, there have been nearly 50,000 cases in Norway, and about 150,000 cases in the Netherlands, which has three times the population of Norway. In the Netherlands, death from diphtheria now runs barely behind the mortality from tuberculosis in spite of the increase of the latter disease. Only Great Britain and Hungary, where immunization had been pushed to the limit, experienced no rise whatever.

It is pointed out that even oceans constitute no effective barrier against a carrier disease like diphtheria. The lesson drawn is that immunization can be safely relaxed only when diphtheria has been eradicated.

The New York Rheumatism Association held its annual meeting at the New York Academy of Medicine, May 9, under the presidency of Dr. Russell L. Cecil, F.A.C.P.

Among the speakers were Dr. John Lansbury, F.A.C.P., Philadelphia, "Dietary Deficiency in the Etiology of Interstitial Calcinosis"; Dr. Eugene F. Trout, F.A.C.P., Chicago, "Bone Marrow Findings in Arthritis"; Lt. Col. Philip S. Hench, F.A.C.P. and Major Edward W. Boland (Associate), "Rheumatic Centers of the U. S. Army"; Dr. Abraham S. Gordon, F.A.C.P., Brooklyn, "Transmission of Gold Salts to the Fetus through the Placenta"; and Capt. Joseph L. Hollander (Associate), et al., "Acute Arthritis Resembling Reiter's Syndrome."

Dr. George B. Dorff, F.A.C.P., Brooklyn, recently received a special citation for his work with the Selective Service of Brooklyn. Dr. Dorff is the retiring president of the East New York Medical Society.

Under the presidency of Elihu S. Wing, F.A.C.P., Providence, Rhode Island, the Rhode Island Medical Society held its 134th Annual Session of May 16–17. Dr. Wing's presidential address was entitled, "Medical Care in Rhode Island."

Among guest speakers on the program were Dr. Stanley P. Reimann, F.A.C.P., Philadelphia, Dr. Roger I. Lee, F.A.C.P., Dr. Elliott P. Joslin, F.A.C.P., and Dr. Samuel A. Levine, F.A.C.P., the latter three of Boston.

Dr. Francis G. Blake, F.A.C.P., dean and Sterling professor of Medicine at Yale University School of Medicine, delivered the Chapin Oration on "Some Recent Advances in the Control of Infectious Diseases."

Dr. Josiah J. Moore, F.A.C.P., president of the Chicago Medical Society and treasurer of the American Medical Association, delivered the commencement address of the Montana State University, Missoula, earlier this month, and was awarded the honorary degree of Doctor of Laws. Dr. Moore is an alumnus of this institution.

Col. Thomas T. Mackie, F.A.C.P., (MC), AUS, has been reëlected president of the American Foundation for Tropical Medicine. The Foundation received during 1944, $47,350 from various sources toward its work. Of this total, $38,760 have been given in eleven grants to medical schools and other institutions for teaching and research purposes.

A. C. P. Postgraduate Courses, Autumn 1945

The Executive Offices of the College and the Committee on Postgraduate Courses have been engaged in formulating a program of Postgraduate and Refresher Courses for the autumn of 1945, but much work is involved before all courses can be definitely announced.

The following is the tentative program, although specific dates cannot yet be announced—it is expected that these courses will be given between the end of September and December 15:

1. Cardiology

   One course of one week, November 5–10, under Dr. Paul D. White, Director, Massachusetts General Hospital and Harvard University; this is a repetition of Dr. White's course given during the autumn of 1944, and is given primarily for those members of the College who were unable to obtain admission to the previous course. This course already has applications on file practically to its capacity. No non-members can be accommodated.

One course in Advanced Cardiology for a more limited group is under consideration, and two different institutions and directors have been approached; final report will be published later.

2. Allergy

A one week course in Allergy, probably during October, will be given by Dr. Robert A. Cooke, Director, at the Roosevelt Hospital, New York City; this will be essentially a repetition of Dr. Cooke's course given for the College during the autumn of 1944.

3. General Medicine

A one week's course by Dr. Homer P. Rush, Director, University of Oregon Medical School; essentially a repetition of Dr. Rush's course given during the autumn of 1944.

4. Internal Medicine

One or two courses planned, each of two weeks' duration; under consideration are courses at the University of Michigan Medical School, Northwestern University Medical School, and the University of Texas Medical Branch. Announcements will be made later.

Other requests for courses, under consideration, include:

Endocrinology

Under Dr. Willard O. Thompson, Director, Chicago

Gastro-enterology or Internal Medicine

Under Dr. Walter L. Palmer, Director, Chicago

Physiology of Disease
Tropical Medicine
Metabolic Diseases
Nutrition

Members of the College are requested to send in their suggestions and recommendations to the Executive Secretary of the College, Mr. E. R. Loveland, 4200 Pine Street, Philadelphia 4, Pa.

Committee on Postwar Medical Service

The Joint Committee on Postwar Medical Service meets monthly in Chicago. Representatives on the Joint Committee come from the American Medical Association, the American College of Physicians, the American College of Surgeons, and many other interested organizations.

The full minutes of these meetings are published in The Journal of the American Medical Association, and therefore are not repeated in the Annals of Internal Medicine.

Minutes of the meeting held at Chicago on March 17 are the last available when this copy goes to press. Of particular importance was the report of Lt. Col. Lueth on the replies to questionnaires that had been distributed to medical officers. Forty-seven per cent have indicated that they desire to return to practice in their former communities after the war; more than 21 per cent indicated they do not plan to re-engage in practice in their former communities. Less than half of this latter group, however, gave a definite locality in which they would like to practice after the war.

Lt. Col. Lueth made an extensive report on the analysis of those interested in Industrial Medical Practice and of Economic Aspects of Postwar Practice. His report is published in The Journal of the American Medical Association, issue of May 12, 1945, page 138.

Other items under discussion included: Report on Educational Internship and Residency Opportunities for Medical Officers; activities of the Bureau of Information, a clearing bureau for all sorts of information to medical officers; Local Organization of Courses for Graduate Study; Report of the Subcommittee to Draw Up Recommendations to the Governors of the States (the draft of a letter was approved, placing the facilities of the Committee on Postwar Medical Service at the disposal of the Governors of the States, and making certain helpful suggestions concerning the provisions of Public Law 346, 78th Congress—the G. I. Bill of Rights—as they may affect the entire field of medical education; the Governor of each State is vested with the power and duty of certifying to the Veterans' Administration the institutions in his state which are qualified to give acceptable courses of education and training in each of many categories); Progress Report of Subcommittee on Surplus Medical and Hospital Supplies; Progress Report on Laws concerning Temporary Licensure; Formulation of Lists of Medical Officers to be Considered for Demobilization; Report of Subcommittee on Establishment of Medical Corps in the Veterans' Administration; Report of Subcommittee on Enrolment of Medical Students; and Informational Reports.

A meeting of the Joint Committee was held at Chicago on May 12, minutes of which will be published as soon as available.

War-Time Graduate Medical Meetings

The activities of the War-Time Graduate Medical Meetings, of which the American College of Physicians is co-sponsor, have been prosecuted with increasing vigor in many sections during the first four months of the current year. This is gratifying in view of the restrictions of medical meetings generally caused by the regulation of the Office of Defense Transportation. The Surgeons General and the Office of Defense Transportation have recognized the valuable function performed by these meetings and consequently have been very liberal in their granting privileges of convention.

The Central Committee is hopeful that the civilian physicians will continue their coöperative support. It is recognized that the continuation of the war is producing increasingly greater strain on civilian physicians. While this activity is entirely a voluntary effort, we hope that none of us will become weary in well doing. Any information or opinions concerning the stimulation of activities of the War-Time Graduate Medical Meetings will be appreciated by the Central Committee.

George Morris Piersol, M.D. (American College of Physicians)
Alfred Blalock, M.D. (American College of Surgeons)
F. F. Borzell, M.D. (American Medical Association), Chairman

War-Time Graduate Medical Meetings

Region No. 5 (Maryland, District of Columbia, Virginia, West Virginia)—Dr. J. A. Lyon, Chairman; Dr. C. R. Edwards, Dr. C. B. Conklin.

A. A. F. Regional Hospital, Langley Field, Virginia

June 29 Gastro-enterology—Dr. Lay Martin.
Traumatic Surgery of the Abdomen—Lieutenant R. C. Wood.

Newton D. Baker General Hospital, Martinsburg, West Virginia

June 18 Liver Diseases Seen in the Present War—Colonel Balduin Lucke.

REGION No. 14 (Indiana, Illinois, Wisconsin)—Dr. W. O. Thompson, Chairman; Dr. N. C. Gilbert, Dr. W. H. Cole, Dr. W. D. Gatch, Dr. R. M. Moore, Dr. H. M. Baker, Dr. E. R. Schmidt, Dr. E. L. Sevringhaus, Dr. F. D. Murphy.

Gardiner General Hospital, Chicago, Illinois

June 20 Chest Diseases and Diseases of the Larynx.
June 27 Low Back Pain.
July 11 Heart Disease and Allied Conditions.
July 18 Bone and Joint Infections.
July 25 Arterial Vascular Disease—Traumatic Lesions.

Station Hospital, Fort Sheridan, Illinois

June 20 Heart Disease and Allied Conditions.
June 27 Bone and Joint Infections.
July 11 Arterial Vascular Disease—Traumatic Lesions.
July 18 Repair of Bone in Fractures and Diseases.
July 25 Diseases of the Kidneys—Urogenital Tract.

Mayo General Hospital, Galesburg, Illinois

June 20 Arterial Vascular Disease—Traumatic Lesions.
June 27 Repair of Bone in Fractures and Diseases.
July 11 Diseases of the Kidneys—Urogenital Tract.
July 18 Blood Dyscrasias—Malaria—Filariasis.
July 25 High Blood Pressure.

Vaughan General Hospital, Hines, Illinois

June 20 Diseases of the Kidneys—Urogenital Tract.
June 27 Blood Dyscrasias, Malaria, Filariasis.
July 11 High Blood Pressure.
July 18 Laboratory Diagnosis and Its Relationship to Medical and Surgical Treatment.
July 25 Conditions Affecting Glucose Metabolism.

Station Hospital, Camp Ellis, Illinois

June 20 High Blood Pressure.
June 27 Laboratory Diagnosis and Its Relationship to Medical and Surgical Treatment.
July 11 Conditions Affecting Glucose Metabolism.
July 18 Brain and Spinal Cord Injuries.
July 25 Diseases of the Intestinal Tract—Medical and Surgical Diagnosis and Care.

Station Hospital, Camp McCoy, Wisconsin

June 20 Conditions Affecting Glucose Metabolism.
June 27 Brain and Spinal Cord Injuries.
July 11 Diseases of the Intestinal Tract—Medical and Surgical Diagnosis and Care.
July 18 Plexus and Peripheral Nerve Injuries.
July 25 Dermatological Diseases.

Station Hospital, Truax Field, Wisconsin

June 20 Dermatological Diseases.
June 27 Burns and Plastic Surgery.
July 11 Malignancies in the Army Age Group—Medical X-Ray and Surgical Diagnosis and Treatment.
July 18 Endocrinology.
July 25 Virus and Rickettsial Diseases—Medical and Neurological Diseases and Treatment.

Station Hospital, Chanute Field, Illinois

June 20 Virus and Rickettsial Diseases—Medical and Neurological Diseases and Treatment.
June 27 Psychosomatic Medicine.
July 11 Wound Healing and Tendon Surgery.
July 18 Mental Hygiene and the Prevention of Neuroses in War.
July 25 Thrombosis, Thrombophlebitis and Anticoagulants in Less Common Peripheral Vascular Diseases.

Billings General Hospital, Indiana

June 20 Wound Healing and Tendon Surgery.
June 27 Mental Hygiene and the Prevention of Neuroses in War.
July 11 Thrombosis, Thrombophlebitis and Anticoagulants in Less Common Peripheral Vascular Diseases.
July 18 Peptic Ulcer, Gall Bladder and Liver Diseases.
July 25 Low Back Pain.

Wakeman General Hospital, Indiana

June 20 Thrombosis, Thrombophlebitis and Anticoagulants in Less Common Peripheral Vascular Diseases.
June 27 Peptic Ulcer, Gall Bladder and Liver Diseases.
July 11 Low Back Pain.
July 18 Chest Diseases and Diseases of the Larynx.
July 25 Bone and Joint Infections.

Region No. 23 (Nevada, Northern California)—Dr. S. R. Mettier, Chairman; Dr. E. H. Falconer, Dr. D. N. Richards.

U. S. Naval Hospital, Mare Island, California

June 15 The Surgical Approaches to the Knee Joint—Dr. LeRoy C. Abbott.

Station Hospital, Fort Ord, California

June 16 Abdominal Surgery—Dr. Thomas F. Mullen.
June 23 Injuries to the Knee Joint—Dr. Frederic C. Bost.

Station Hospital, Camp Roberts, California

June 16 Severe Infections of the Hand—Dr. Edmond D. Butler.
June 23 Experiences with Infectious Diseases in Army Camps in England—Dr. Gordon E. Hein.

Station Hospital, Stockton Army Air Base, California

June 20 Diagnosis and Treatment of Arthritis—Dr. Hans Waine.
June 27 Injuries to the Knee Joint—Dr. Carl E. Anderson.

Dr. Willard O. Thompson, F.A.C.P., Chairman of Regional Committee No. 14 of the War-Time Graduate Medical Meetings, was presented with the following Citation for distinguished service to the Sixth Service Command by Major General Reynolds, Commanding General:

"In 1942 the American Medical Association, in conjunction with the American College of Surgeons and the American College of Physicians, established a fund to provide postgraduate medical instruction for medical officers stationed throughout the Army.

"Dr. Willard O. Thompson, Chairman of the Committee for War-Time Graduate Medical Meetings for Region No. 14 which includes Illinois and Wisconsin, obtained the services of prominent teachers and practitioners of medicine to lecture and conduct clinical exercises in the hospitals of the Sixth Service Command. He himself has actively participated in the teaching and by his boundless energy and enthusiasm has maintained the continuity and high quality of the program. The medical officers of this Service Command as well as hundreds of civilian physicians who have attended the courses at Army hospitals have universally expressed their appreciation for this unusual opportunity for postgraduate instruction which has definitely raised the standard of medical practice in the Sixth Service Command.

"Dr. Thompson, as Chairman of the Committee, by his untiring efforts and devotion to this important program, has rendered distinguished service to the Sixth Service Command and in recognition thereof the Commanding General is pleased to present this Citation."

Vice Admiral Ross T. McIntire, (MC), Surgeon General of the U. S. Navy, commenting on the programs of the War-Time Graduate Medical Meetings in Zone Number Five, recently wrote to the local Chairman, Dr. James Alexander Lyon, of Washington: "The scope and general interest of the subjects presented, as well as the fact that such outstanding members of the medical profession participated so generously, are noteworthy. This represents a real contribution to the morale and training of the medical officers who have had and are still having the opportunity to profit from these courses.

"One hears so often that medical officers on active duty are fearful of getting out of touch with current medical events. These War-Time Graduate Medical Meetings seem to have been designed to anticipate just such a situation, and have succeeded admirably."

OBITUARIES

DR. MORRIS WEISSBERG

Dr. Morris Weissberg, F.A.C.P., died in Brooklyn, New York, on March 17, 1945. Dr. Weissberg had been a Fellow of the American College of Physicians since 1926. He was born in Russia in 1887, received his medical degree from the Long Island College Hospital. For many years he was on the Staff of the Bushwick Hospital of Brooklyn, and Attending Physician, Evangelical Deaconess Hospital. He was Consultant to the St. Luke's (Newburgh) Hospital and Evangelical Home for the Aged for a number of years. He served in the first World War as 1st Lieutenant in the A.E.F., was a member of the Medical Society of the County of Kings, American Heart Association, Brooklyn Society of Internal Medicine, Brooklyn Thoracic Society, American Association for the Advancement of Science, Medical Society of the State of New York, American Legion; Fellow, American Medical Association, New York Academy of Medicine; Diplomate, American Board of Internal Medicine.

Dr. Weissberg was a respected member of the profession and his loss will be keenly felt.

ASA L. LINCOLN, M.D., F.A.C.P.,
Governor for Eastern New York

COLONEL JOHN DIBBLE, (MC), U. S. A.

Colonel John Dibble, (MC), U. S. Army, was reported "missing in action" during April 1943. It has now been confirmed, through Major General George F. Lull of the Office of the Surgeon General, that Colonel Dibble was definitely lost. He was in a plane which went down in the harbor of a small island in the Pacific, and only two of those aboard the plane survived.

Colonel Dibble was born in Camden, N. J., May 24, 1890. He graduated from the University of Pennsylvania School of Medicine in 1915, served an internship at the Episcopal Hospital of Philadelphia, and then entered the Army Medical Corps. He took the regulation course in the Army Medical School and in the Army School for Flight Surgeons. He also took postgraduate work at the Mayo Foundation, and a course in military science and tactics at the Army Command and General Staff School. His tours of duty included: assistant, medical service, U. S. Army General Hospital, Fort Bliss, Texas; post surgeon at various Army Station Hospitals; chief of the tuberculosis section of the Walter Reed General Hospital; executive officer, medical service, Letterman General Hospital, San Francisco; chief of medical service, Station Hospital, Fort McKinley, P.I.; chief of medical service, Station Hospital, Fort Sheridan, Illinois; executive officer, Medical Department, Army Field Service School; medical inspector,

Eighth Corps Area. He was rated as an excellent internist, well qualified in tuberculosis work. He was a Fellow of the American Medical Association and a member of the Association of Military Surgeons of the United States. He had been a Fellow of the American College of Physicians since 1941. He was the first member of the College whose life was lost in the war.

DR. THOMAS FRANCIS COTTER

Dr. Thomas Francis Cotter, F.A.C.P., Indiana Harbor, Indiana, died March 12, 1945, of pneumonia, aged 67. He was born at Indianapolis in 1877, and graduated from the Medical College of Indiana in 1902. For some years he was a member of the staffs of Mercy and Methodist Hospitals of Gary and at one time was connected with the U. S. Public Health Service. More recently he was a member of St. Catherine's Hospital.

Dr. Cotter was a member of the Lake County Medical Society and the Indiana State Medical Society. He was a Fellow of the American Medical Association and had been a Fellow of the American College of Physicians since 1925. He enjoyed a good reputation in the community where he practiced, both with the public and with the profession.

ROBERT M. MOORE, M.D., F.A.C.P.,
Governor for Indiana

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